



PHD

## Ruthenium catalysed sequential and tandem reactions

Pridmore, Simon

*Award date:*  
2009

*Awarding institution:*  
University of Bath

[Link to publication](#)

## Alternative formats

If you require this document in an alternative format, please contact:  
[openaccess@bath.ac.uk](mailto:openaccess@bath.ac.uk)

Copyright of this thesis rests with the author. Access is subject to the above licence, if given. If no licence is specified above, original content in this thesis is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC-ND 4.0) Licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). Any third-party copyright material present remains the property of its respective owner(s) and is licensed under its existing terms.

### Take down policy

If you consider content within Bath's Research Portal to be in breach of UK law, please contact: [openaccess@bath.ac.uk](mailto:openaccess@bath.ac.uk) with the details. Your claim will be investigated and, where appropriate, the item will be removed from public view as soon as possible.

# **Ruthenium Catalysed Sequential and Tandem Reactions**

Simon John Pridmore

A thesis submitted for the degree of Doctor of  
Philosophy

University of Bath

Department of Chemistry

June 2009

## **COPYRIGHT**

Attention is drawn to the fact that copyright of this thesis rests with its author. A copy of this thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with the author and they must not copy it or use material from it except as permitted by law or with the consent of the author.

This thesis may be made available for consultation within the University Library and may be photocopied or lent to other libraries for the purpose of consultation.

Signed..........

Date.....05/06/09.....

## Acknowledgements

I would first like to acknowledge Prof. Jonathan Williams for giving me the opportunity to work with him over the last 4 or so years. I am grateful and indebted to Jon for his constant guidance, encouragement and help towards my research projects. Thanks to Jon for his ideas and enthusiasm for the projects I've worked on and allowing me complete freedom to pursue various avenues of research (mostly unsuccessful!) Outside of the lab I will miss our random chats about stuff that isn't related to chemistry is any way, such as how much deuterated water would you need to give a person to drink before they die. And thanks Jon for letting me attend numerous conferences both home and abroad. It has been emotional!

Thanks to the Williams group past and present for making my time at Bath a blast. Nathan, Duncan, Gareth A, Haniti, Stefan, Mike Nikki, Liana, James Gareth, Tracy and Ory. I'm particularly grateful to Dr Paul Slatford for his endless help around the lab and for his help with the work contained in this thesis and also to Aurelié Daniel who helped immensely with the pyrrole chemistry. Thanks also to the guys next door, Iwan, Paul, Caroline and Rob for providing lots of cups of strong coffee.

"The Boys" Ben, Steve, Tom and Olly thanks for countless nights out and general debauchery and laughs. Also to "boys lunch" which made the writing up a little less painful.

To the mighty Chemistry FC, We finally won the league after 10 seasons! Thanks to all the players past and present for making Friday afternoons a complete write off and the truly memorable nights out in Bath.

I'd wish to thank my parents for their unwavering support and help throughout my education without them I wouldn't be here today. Finally thank you to my gorgeous girlfriend Liz for your support and love right the way through my PhD and write up, I love you.

## SYNOPSIS

This thesis describes the chemistry developed during a study of novel transition metal-catalysed reactions.

**Chapter 2** describes a novel procedure for the synthesis of 2,5-disubstituted furans *via* the isomerisation of 1,4-alkyne diols, avoiding the pitfalls of the traditional Paal-Knorr reaction. The initial ruthenium catalysed isomerisation is followed by an *in situ* cyclocondensation reaction using an acid co-catalyst in a one step route to furan derivatives. In addition the synthesis of the 1,4-dicarbonyl surrogates, 1,4-alkyne diols, is detailed.

The methodology detailed in chapter 2 is then used in the synthesis of pyrrole derivatives in **Chapter 3**. Replacement of the acid co-catalyst with 2 equivalents of amine allow various pyrrole derivatives to be synthesised using the 1,4-alkynediols as starting materials. Various amines can also be used from anilines, benzylamines and aliphatic amines, allowing access to a wide range of products.

**Chapter 4** describes the attempted isomerisation of propargylic alcohols in a route to  $\alpha,\beta$ -unsaturated esters. Using the tandem oxidation (with a sacrificial hydrogen acceptor)/decarboxylative Knoevenagel condensation of alcohols various  $\alpha,\beta$ -unsaturated ester derivatives were synthesised. Further optimisation allowed the fully saturated, doubly homologated ester derivatives to be synthesised using the “borrowing hydrogen” methodology

## ABBREVIATIONS

Å	Angstroms
Ac	Acetyl
Ar	Aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	Boiling point
Bn	Benzyl
CI	Chemical ionisation
Cod	1,5-cyclooctadiene
Cp*	Pentmethylcyclopentadienyl
DCM	Dichloromethane
DME	Ethylene glycol dimethylether
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPE	Diphenylether
DPE-Phos	Bis(2-diphenylphosphinophenyl)ether
DPF-Phos	4,6-bis(diphenylphosphino)dibenzo furan
DPEN	Diphenylethylenediamine
DPPB	1,4-Bis(diphenylphosphino) butane
DPPE	1,2-Bis(diphenylphosphino) ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DPPM	Diphenylphosphino methane
DPPP	1,3-Bis(diphenylphosphino) propane
ee	Enantiomeric excess
EI	Electron impact
GC	Gas Chromatography
h	Hours
Hz	Hertz
IR	Infrared

<i>i</i>	<i>Iso</i>
<i>J</i>	Coupling Constant
LC	Liquid Chromatography
<i>m</i>	<i>Meta</i>
Me	Methyl
Mes	Mesityl (1,3,5-trimethylphenyl)
m.p.	Melting Point
MPV	Meerwein-Ponndorf-Verley
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
<i>o</i>	<i>Ortho</i>
<i>p</i>	<i>Para</i>
Ph	Phenyl
ppm	Part Per Million
psi	Pounds per Square Inch
Py	Pyridine
RCM	Ring Closing Metathesis
rt	Room temperature
<i>t</i> Bu	<i>Tert</i> -Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl (methylphenyl)
TPAP	Tetra- <i>n</i> -propylammonium perruthenate
TsDPEN	<i>N</i> -(Toluenesulfonyl)diphenylethylenediamine
TsOH	Toluenesulfonic acid
TLC	Thin Layer Chromatography
UV	Ultraviolet

## CONTENTS

<b>Acknowledgements</b>	<b>i</b>
<b>SYNOPSIS</b>	<b>ii</b>
<b>ABBREVIATIONS</b>	<b>iv</b>
<b>1 INTRODUCTION</b>	<b>1</b>
1.1 Sequential reactions	1
1.2 Transfer hydrogenation	7
1.3 Paal-Knorr heterocycle synthesis	19
1.4 Meyer-Schuster-Rupe rearrangements and redox isomerisations	29
1.5 Knoevenagel Condensation	35
1.6 References	39
<b>2 RESULTS AND DISCUSSION I</b>	<b>45</b>
2.1 Background	45
2.2 Aims	48
2.3 Initial studies - Isomerisation of 1,4-alkyne diols	48
2.4 Ruthenium catalysed isomerisation of 1,4-alkyne diols	51
2.5 Optimisation	53
2.6 Acid Screen	54
2.7 Synthesis of 1,4-alkyne diols	56
2.8 Synthesis of 2,5-disubstituted furans	58
2.9 Chapter summary	61
2.10 References	62
<b>3 RESULTS AND DISCUSSION II</b>	<b>63</b>
3.1 Aims	63
3.2 Background	63
3.3 Initial studies	64
3.4 Optimisation	67
3.5 Amine loading screen	68
3.6 Synthesis of <i>N</i> -2,5-substituted pyrroles	71
3.7 Synthesis of <i>N</i> -2,5-substituted pyrroles: Amine scope	73
3.8 Synthesis of <i>N</i> -2,5-substituted pyrroles: Amine scope II	74

3.9	Chapter summary	76
3.10	References	77
<b>4</b>	<b>RESULTS AND DISCUSSION III</b>	<b>78</b>
4.1	Aims	78
4.2	Background	78
4.3	Isomerisation of propargylic alcohols	79
4.4	Alkenes from alcohols	82
4.5	Aims	82
4.6	Background	82
4.7	Optimisation	85
4.8	Synthesis of alkenes from alcohols: tandem hydrogen transfer/condensation	88
4.9	Initial studies	91
4.10	Optimisation	92
4.11	Synthesis of alkanes from alcohol <i>via</i> “borrowing hydrogen	99
4.12	Chapter Summary	101
4.13	References	102
<b>5</b>	<b>EXPERIMENTAL</b>	<b>104</b>
5.1	General experimental methods	104
5.2	Experimental procedures: Chapter 2	106
5.3	Experimental procedures: Chapter 3	133
5.4	Experimental procedures: Chapter 4	157
5.5	References	178
<b>APPENDIX</b>		
	Publications to date	179



## 1 INTRODUCTION

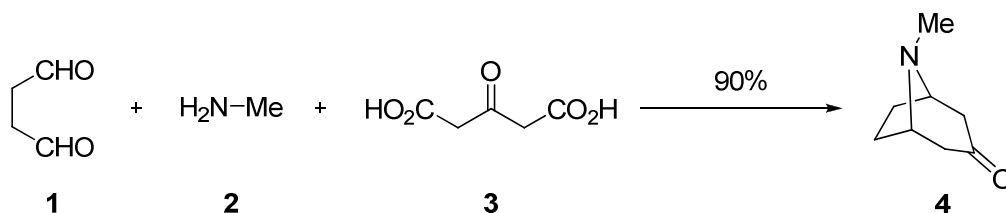
### 1.1 Sequential Reactions

The conventional approach for the synthesis of organic molecules is the stepwise formation of individual bonds to attain the desired target. The major concern with this classical approach is the total yield of the desired product after the final step. Such a process requires the purification and isolation of multiple intermediates through multiple experimental steps. As the number of steps increases there is an incremental loss of yield at each step thus lowering efficiency in the desired route to the target molecule. Therefore increasing synthetic efficiency is at the forefront of challenges facing organic chemists. With chemical production on the large scale there are concerns regarding such multistep reactions with the consumption of both natural and man-made resources and use of energy along with concerns about handling the waste from such processes. In the face of tough legislation regarding the disposal of waste and emissions, and the ever increasing concern of climate change, replacement of multistep organic synthesis with efficient catalysed reactions with high atomic efficiency is having a significant impact on the synthesis of pharmaceuticals and fine chemicals.

The combination of multiple reactions in a single pot is a powerful tool in achieving the target of improved synthetic efficiency. Sequential reactions offer a number of opportunities to improve chemical transformations by accomplishing two or more synthetic steps in one pot. With one-pot reactions comes increased operational simplicity as well as reduction in energy and materials usage and waste output, with the purification of intermediates at each step no longer needed. The use of sequential reactions has obvious benefits both environmentally and economically. Such advantages have attracted much research in the area over the last decade with a vast number of publications in the area. The area of sequential reactions has been subject to many comprehensive reviews.<sup>1-4</sup>

There are two main types of sequential reaction; Tandem reactions and consecutive reactions. Tandem (also domino, cascade) reactions have been defined by Tietze as “*A process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation*

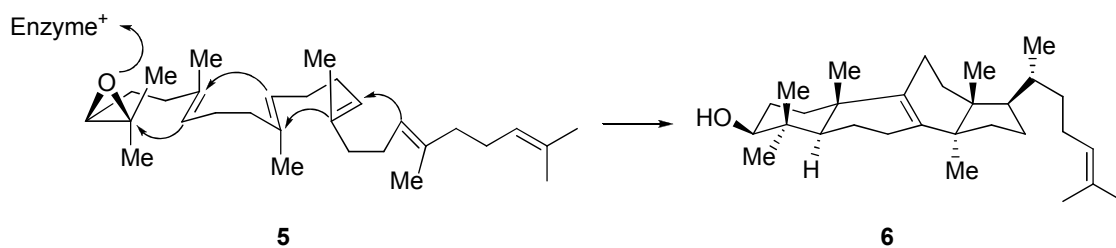
in the previous step”.<sup>2</sup> Such a reaction is Robinson’s classic synthesis of tropinone. Characteristic of a tandem reaction there is no further addition of reagents or modification of conditions on commencement of the reaction. In Robinson’s synthesis of tropinone succinaldehyde **1**, methylamine **2** and acetonedicarboxylic acid **3** undergo a double Mannich reaction followed by a double decarboxylation reaction to furnish tropinone **4** in good yield (**Scheme 1**).<sup>5</sup>



**Scheme 1.** Robinson’s tandem synthesis of tropinone.

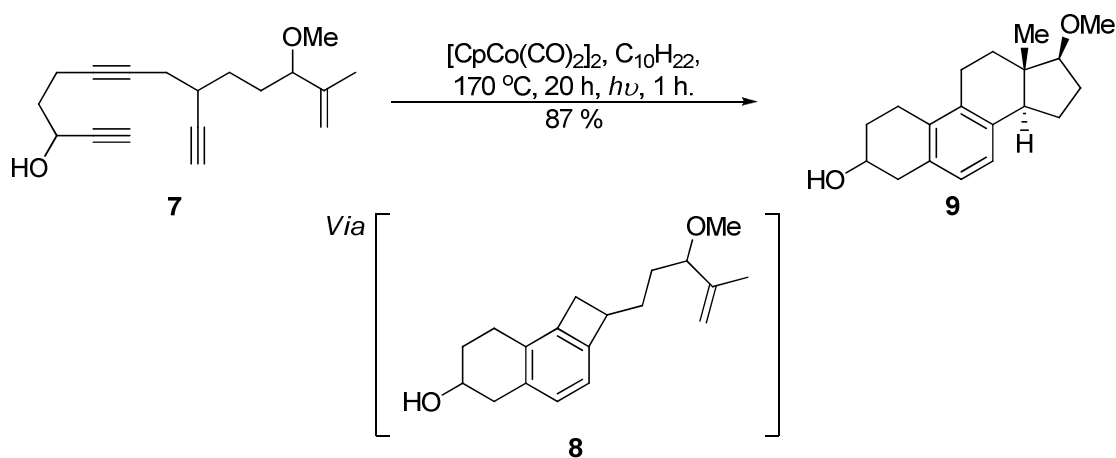
Consecutive reactions differ from tandem reactions in that another reagent, mediator, catalyst or reaction condition is added or used after the initial transformation without purification of the first formed product. The subsequent reaction steps then lead to the final product. Whilst some operational simplicity is lost, the benefits associated with tandem reaction remain. Indeed consecutive reactions are especially useful for synthetic routes involving inherently unstable reactive intermediates.

In Nature cascade reactions are common. The enzyme mediated biosynthesis of lanosterol **6**, an important intermediate in the synthesis of steroids, is achieved from squalene epoxide **5** and is an exquisite example of a cascade reaction in Nature. The reaction results in the formation of four C-C bonds and six stereogenic centres *via* a carbocationic cascade reaction<sup>6</sup> (**Scheme 2**). Such reactions have been exploited by chemists in the biomimetic synthesis of steroids.<sup>7</sup>



**Scheme 2.** Biosynthesis of lanosterol **6** from squalene epoxide **5**.

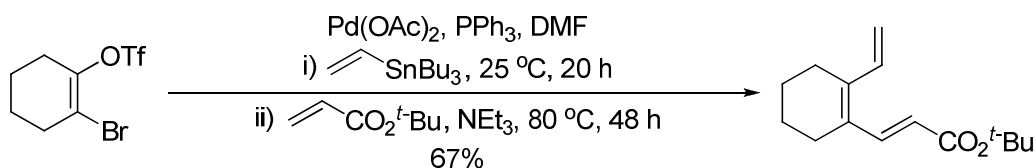
Cascade reactions can be distinguished by the mechanism of the combined steps by considering the eight reaction types: cationic, anionic, radical, pericyclic, photochemical, carbenoid, transition metal catalysed and oxidation/reduction. A cascade reaction can possess any combination of these reaction types with any number of steps. Beautiful work by Vollhardt<sup>8</sup> and co-workers encompasses the methodology of the cascade reaction, and is shown in the synthesis of steroids with an aromatic B ring in only one step from an acyclic precursor **7** using  $\text{CpCo}(\text{CO})_2$  as catalyst (**Scheme 3**). The whole process involves a transition metal mediated alkyne cyclisation with formation of the cyclobutahydronaphthalene **8** followed by an electrocyclic ring opening and intramolecular Diels-Alder reaction to yield the steroid derivative **9** in a transition metal catalysed-photochemical cascade reaction.



**Scheme 3.** Vollhardt's cascade synthesis of steroids.

Initially, research into transition metal catalysis concentrated on the development of a single, highly selective, high yielding step. With the plethora of carbon-carbon, carbon-hydrogen and carbon-heteroatom bond forming reactions known, metal catalysts have subsequently found favour in sequential reactions. Many transformations where a single catalyst is used to conduct two or more mechanistically similar reactions have been reported and reviews published.<sup>9,10</sup>

Unsurprisingly, palladium catalysts have been employed in the majority of metal catalysed sequential reactions. De Meijere<sup>11</sup> utilised a palladium catalyst to effect two cross coupling reactions in one-pot. After an initial coupling of a vinyl triflate a subsequent coupling of vinyl bromide achieved (**Scheme 4**). Although this reaction is an example of a consecutive reaction, with the second Heck coupling step requiring a change in conditions it shows the synthetic utility of such a reaction.



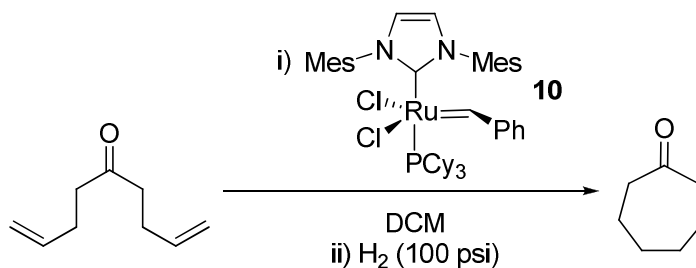
**Scheme 4.** Consecutive palladium catalysed cross coupling reaction.

More recently a new, but related area of research has sought to use a single catalyst for one or more transformations in one pot. This area has great potential as there are many catalytic reactions that could be linked together in sequence. The first reported reactions of this type were sequential reactions performed by a single catalyst in a single pot. In these cases addition of a new reagent or a change in conditions causes the nature of the catalyst to change, such that it may no longer catalyses the first reaction but remains catalytically active for the next step.

The ruthenium metathesis catalysts developed by Grubbs and co-workers<sup>12</sup> have proven to be very effective in these types of single catalyst sequential reactions. McLain and co-workers found that an ethylene/methacrylate copolymer formed by ring-opening

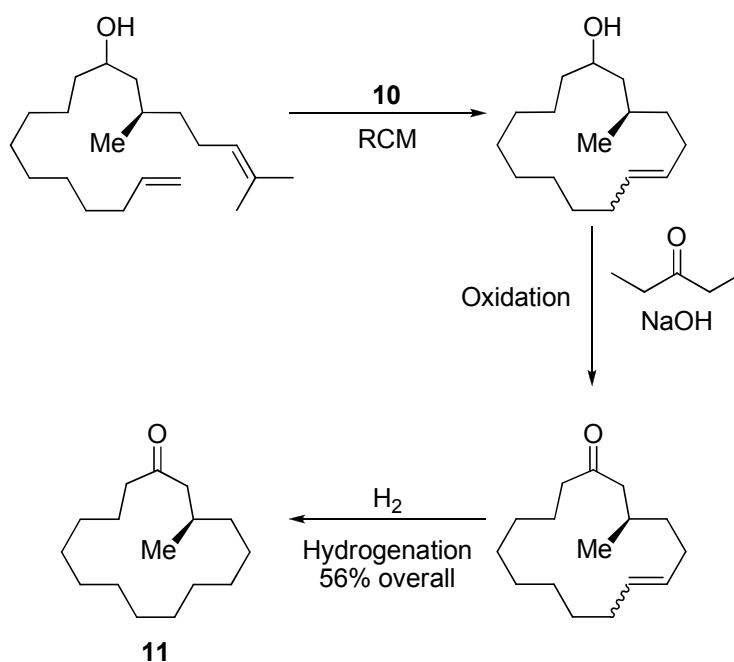
metathesis polymerisation using Grubbs' "1<sup>st</sup> generation" catalyst could be successfully hydrogenated simply by placing the reaction vessel under an atmosphere of hydrogen (400 psi) after the polymerisation took place.<sup>13</sup> Studies by Fogg have shown that the treatment of the catalyst with hydrogen forms the known hydrogenation catalyst  $\text{RuCl}_2(\text{H}_2)(\text{PCy}_3)_2$ .<sup>14</sup>

The research group of Grubbs was quick to utilise the findings of McLain and Fogg, and used this methodology in a small molecule synthesis.<sup>15</sup> They showed that first or second generation **10** metathesis catalysts were able to mediate either ring-closing or cross metathesis followed by hydrogenation (**Scheme 5**).



**Scheme 5.** Sequential RCM/hydrogenation reaction.

In an extension of the concept, Grubbs also found that these complexes act as a pre-catalyst for both the oxidation of alcohols and the reduction of ketones *via* transfer hydrogenation. Addition of base and a suitable hydrogen donor such as 2-propanol, led to reduction of ketones, or a suitable acceptor such as 3-pentanone led the oxidation of alcohols. Grubbs demonstrated this unprecedented trifunctional catalyst in the synthesis of (*R*)-(-)-muscone **11** (**Scheme 6**), in which RCM (ring closing metathesis) followed by oxidation followed by hydrogenation was achieved with a single catalyst in one pot.<sup>15</sup>



**Scheme 6.** Synthesis of (*R*)-(-)-muscone via a novel trifunctional catalyst.

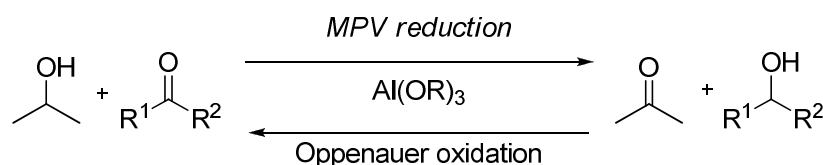
The rapidly increasing understanding and tailoring of transition metal catalysed reactions will certainly in future be responsible for the development of more complex methods for both sequential (tandem, cascade, domino) and concurrent catalysis. Whilst there is a limit on the degree of complexity it is possible to achieve in a single process, multifunctional catalysts provide an invaluable tool for increasing complexity whilst overcoming the downfalls of traditional chemical synthesis.

## 1.2 Transfer Hydrogenation

Oxidation and reduction are amongst the most essential of chemical reactions and of importance in organic synthesis with regards to functional group interconversions. A reaction that causes a decrease in electron ownership of carbon is an oxidation. The change in electron ownership results from either bond formation between carbon and a more electronegative atom, or bond breaking between carbon and a less electronegative atom. The process of reduction is the complementary reverse to oxidation.

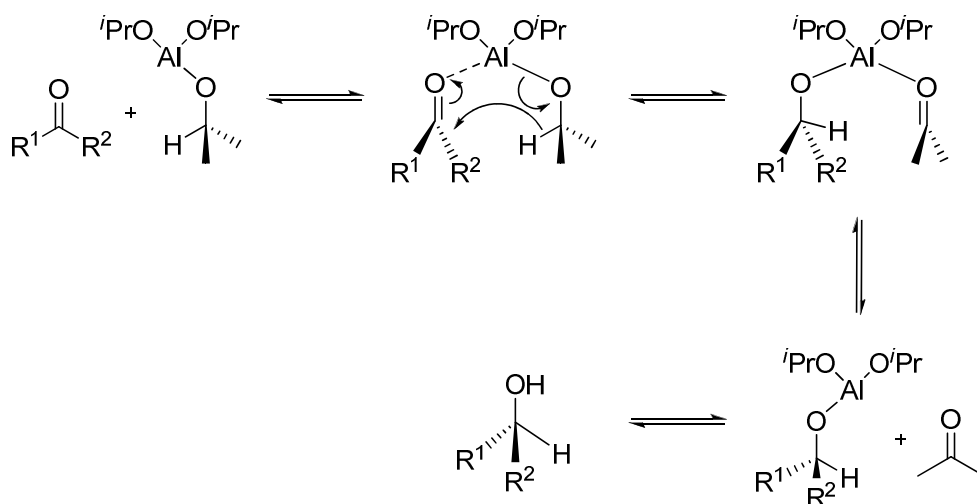
While the majority of metal catalysed and metal mediated oxidations are irreversible and unselective processes, in some cases equilibrium exists between oxidised and reduced species. The first example of such an equilibrium reaction is the aluminium-mediated interconversion of alcohols and carbonyl compounds. Much of the pioneering work into these equilibrium reactions was carried out in the 1920s and it was Meerwein and co-workers who first discovered that chloral was reduced in the presence of aluminium ethoxide and ethanol as solvent.<sup>16</sup> Verley<sup>17</sup> disclosed that butyraldehyde was also a suitable substrate and Ponndorf demonstrated that secondary alcohols could be prepared from ketones in the presence of aluminium isopropoxide.<sup>18</sup> As a result this reaction became known as the Meerwein-Ponndorf-Verley (MPV) reduction.

In 1937, Oppenauer<sup>19</sup> reported that the reverse process (alcohol to carbonyl compound) was also mediated by aluminium alkoxides. Subsequently this reaction became known as the Oppenauer oxidation. Both reactions are completely reversible and in order to drive the equilibrium towards the desired product an excess of hydrogen donor (isopropanol) or hydrogen acceptor (acetone) is required (**Scheme 7**).



**Scheme 7.** MPV reduction and Oppenauer oxidation.

The MPV and Oppenauer reactions are thought to proceed via an intermediate complex in which the carbonyl and alcohol are bound to the aluminium ion. The alcohol is bound to the metal as an alkoxides and the carbonyl is activated via coordination to the Lewis acidic aluminium(III) centre. This orientation allows hydrogen transfer to the carbonyl via a six membered transition state (**Scheme 8**).<sup>20</sup>



**Scheme 8.** Mechanism of the MPV/Oppenauer reactions.

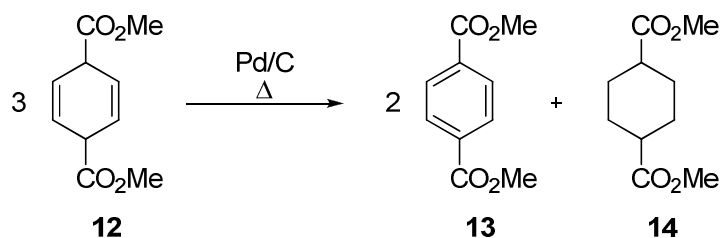
The development of selective oxidants such as the Dess-Martin reagent and metal hydride reducing agents made the use of aluminium alkoxides less important for the reduction of carbonyl compounds. Recently however, improved catalytic systems have overcome the problems associated with these reactions and stimulated research into new aluminium oxidation and reduction reactions. Maruoka and co-workers have utilised bidentate aluminium alkoxides which allow rapid MPV/Oppenauer reactions at catalytic loadings and ambient temperatures.<sup>21,22</sup> More recently Nguyen has reported the use of trimethylaluminium as an effective catalyst in the oxidation of alcohols using benzaldehydes as hydrogen acceptors.<sup>23</sup>

MPV and Oppenauer reactions are among the first examples of transfer hydrogenation reactions. Transfer hydrogenation can be defined as “*the reduction of multiple bonds with the aid of a hydrogen source, other than gaseous hydrogen, in the presence of a catalyst.*” Transfer hydrogenation reactions are appealing since they don’t require the



use of hydrogen gas. Utilising hydrogen donors overcomes the hazardous disadvantages associated with the use of hydrogen gas, such as fire and explosion as well as the high pressures required.

MPV and Oppenauer reactions utilised stoichiometric aluminium reagents which proved to be a disadvantage, emphasised by the slow progress in research to improving these reactions. However catalytic transfer hydrogenation reactions have been known since 1903. Knoevenagel<sup>24</sup> first observed that dimethyl 1,4-dihydroterephthalate **12** disproportionated readily in the presence of palladium black, to yield dimethylterephthalate **13** and *cis* hexahydroterephthalate **14** (Scheme 9).

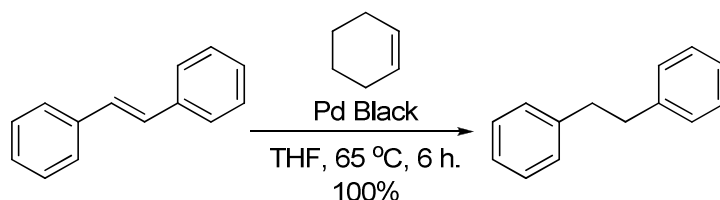


**Scheme 9.** Knoevenagel transfer hydrogenation.

In the following years Wieland<sup>25</sup> observed the same reaction using dihydronaphthalene and predicted that the reaction would occur with the then undiscovered dihydrobenzenes, a prediction confirmed by Zelinski and Pavlov<sup>26</sup> and by Corson and Ipatieff.<sup>27</sup> Despite the seminal works on both the aluminium mediated reactions and the catalytic transfer hydrogenations, development in this area was slow, particularly for donors other than alcohols. The slow progress can be attributed to the limited substrate scope, extended reaction times and low yields. These early transfer hydrogenation reactions have been reviewed in detail<sup>28</sup>

In 1952 Linstead and Braude<sup>29</sup> reported in the journal *Nature* a remarkable breakthrough in transfer hydrogenation methodology. Using cyclohexene as a donor, olefins and

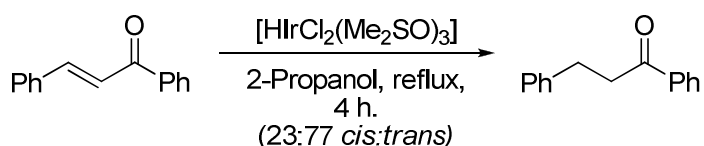
alkynes were reduced in the presence of a heterogeneous palladium catalyst, under relatively mild conditions (**Scheme 10**).



**Scheme 10.** Heterogeneous transfer hydrogenation with an alkene donor.

In further studies, the scope of the reaction was found to extend to reduce aliphatic and aromatic nitro and azo compound to amines, as well as alkynes and alkenes to alkanes. Significantly, carbonyl compounds could also be reduced except when part of an aromatic system (e.g. quinones).<sup>30</sup> Linstead and Braude's research was significant as it was the first example whereby transfer hydrogenation of alkenes was shown to be a viable alternative to reduction with molecular hydrogen.

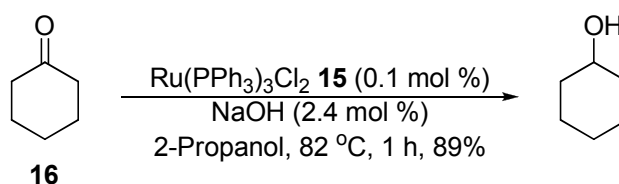
In 1965 Wilkinson<sup>31</sup> reported the first example of a catalytic hydrogenation system utilising  $\text{RhCl}(\text{PPh}_3)_3$  as a homogeneous catalyst. This pioneering research sparked interest into whether transition metal catalysts were viable for homogeneous transfer hydrogenations. Two years later Hensbest<sup>32</sup> reported that an iridium hydride-DMSO complex was capable of reducing C=C bonds in chalcones with excellent chemoselectivity, using 2-propanol as the hydrogen donor (**Scheme 11**).



**Scheme 11.** Hensbest's homogeneous transfer hydrogenation.

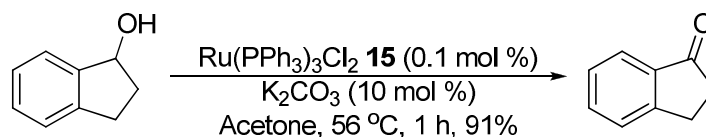
Henbest and Wilkinson's findings prompted an enormous amount of research into homogenous transfer hydrogenations. The most common transition metal transfer hydrogenation catalysts are ruthenium, iridium, rhodium and palladium based complexes, although the complexes of many other elements have shown to be effective. Efforts have been directed into finding catalysts from amongst the less rare metals, particularly nickel<sup>33</sup> and molybdenum<sup>34</sup> but with limited success. It is with ruthenium based systems that the most significant advances have been made. Pioneering work in this area was carried out by Blum who reported the reduction of the olefinic bond in  $\alpha,\beta$ -unsaturated ketones with  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15**.<sup>35</sup> In 1981 Shvo reported the oxidation of secondary alcohols to ketones using a  $\text{Ru}_3(\text{CO})_{12}$  cluster complex with diphenylacetylene as the hydrogen acceptor. Primary alcohols formed dimeric esters under these conditions.<sup>36</sup> Murahashi subsequently reported the formation of lactones from primary alcohols with  $\text{Ru}(\text{PPh}_3)_4\text{H}_2$ .<sup>37, 38</sup> These systems however, suffered from the use of forcing conditions such as high temperature (150-220 °C) hindering their use as synthetically useful systems, but demonstrated the potential utility of metal-mediated transfer hydrogenation reactions.

In 1991, Bäckvall and co-workers reported a significant advance in transfer hydrogenation chemistry. They found that the addition of base to the transfer hydrogenation of cyclohexanone **16** catalysed by  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** resulted in a startling rate enhancement.<sup>39</sup> Further investigation revealed that base was necessary to generate the catalytically active species  $\text{Ru}(\text{PPh}_3)_3\text{H}_2$ .<sup>40, 41</sup> Under these optimised conditions, total conversion could be rapidly achieved under mild conditions in 2-propanol as both hydrogen donor and solvent (**Scheme 12**).



**Scheme 12.** Effect of base in ruthenium catalysed transfer hydrogenation reactions.

Subsequently, the first practical oxidation of secondary alcohols via transfer hydrogenation to ketones was developed by replacing the donor with a suitable acceptor such as acetone (**Scheme 13**).<sup>42</sup>



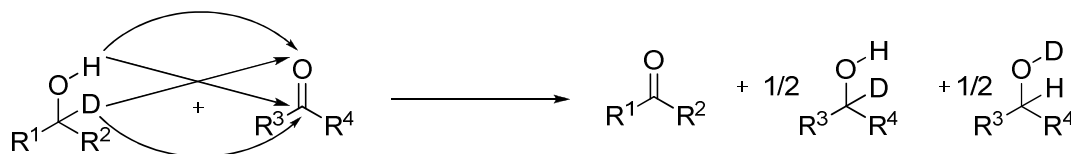
**Scheme 13.** Ruthenium catalysed oxidation of alcohols.

These new, milder reaction conditions allowed for easier mechanistic studies. Bäckvall and co-workers used deuterium labelled compounds and NMR studies to explore the mechanistic pathways of transfer hydrogenation.<sup>43</sup> Two mechanistic pathways are involved, (i) the metal monohydride mechanism, leading to selective carbon to carbon hydrogen transfer or (ii) the non-selective metal dihydride mechanism (**Scheme 14**).

Pathway (i)



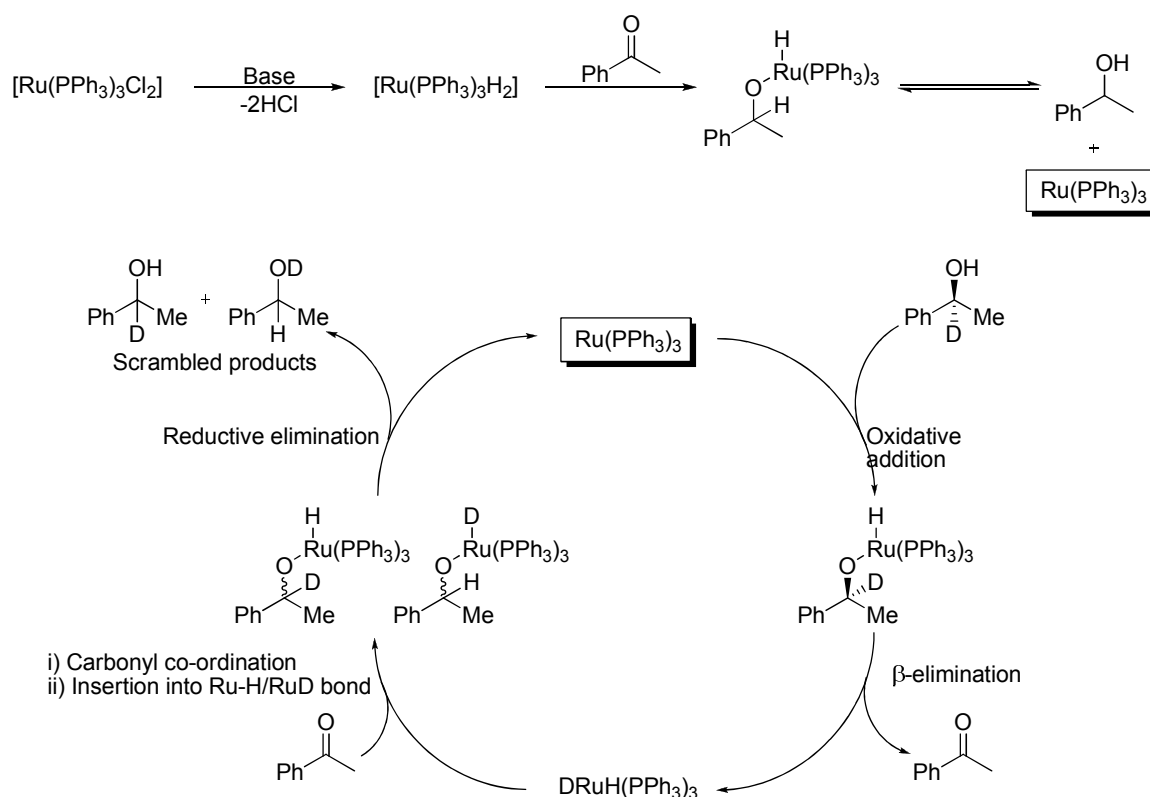
Pathway (ii)



**Scheme 14.** Proposed pathways for transition metal catalysed transfer hydrogenation.

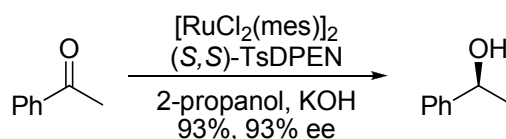
Racemisation studies confirmed that there were indeed two competing pathways, and that the nature of the metal is vital in governing which process takes place. Iridium and rhodium complexes were found to favour the dihydride mechanism, whilst ruthenium

systems proceed via either the monohydride or dihydride mechanism. The following mechanism has been proposed (**Scheme 15**).<sup>44,45</sup>



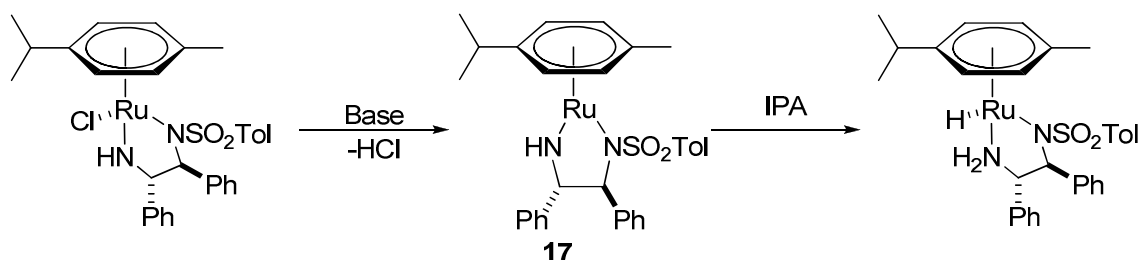
**Scheme 15.** Ruthenium catalysed transfer hydrogenation mechanism.

The most significant advances in the field of asymmetric transfer hydrogenation can be attributed to the group of Noyori, who in 1995 reported the use of a ruthenium pre-catalyst in combination with an enantiomerically pure ligand, monotosylated 1,2-diphenylethylenediamine (TsDPEN) to reduce aromatic ketones with 2-propanol to alcohols at room temperature whilst achieving high enantiomeric excess (**Scheme 16**).<sup>46</sup>



**Scheme 16.** Noyori's asymmetric transfer hydrogenation.

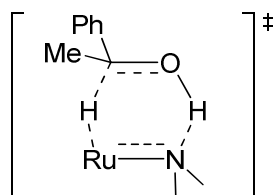
Extensive mechanistic studies revealed that the structure of the catalytically active species was a relatively stable 16-electron complex **17** which when isolated displays excellent activity without the need to add base<sup>47</sup> (**Scheme 17**). This was a significant advance as the system could be applied to base sensitive substrates. This system also immediately found use in the kinetic resolution of secondary alcohols.<sup>48</sup>



**Scheme 17.** Noyori's transfer hydrogenation catalyst.

This system has also been used in conjunction with a formic acid/triethylamine azeotrope as hydrogen donor, allowing the reduction of ketones to be achieved with similarly excellent results under irreversible conditions with liberation of carbon dioxide forcing the equilibrium. This system was subsequently shown to be effective for the asymmetric reduction of imines,<sup>49</sup> an area that had remained undeveloped in comparison with that of carbonyl compounds.<sup>50</sup>

Noyori has postulated that the reaction proceeds *via* direct hydrogen transfer, and has termed the mechanism “metal-ligand bifunctional catalysis”.<sup>51</sup> The mechanism is fundamentally different from the mechanism proposed by Bäckvall, as the ligand is involved in the transfer of a hydride, which has been postulated to occur as a concerted process *via* a cyclic transition state (**Scheme 18**). This mechanism has been subject of extensive experimental and computational analysis.<sup>52, 53</sup>



**Scheme 18.** Proposed transition state for “metal-ligand bifunctional catalysis”.

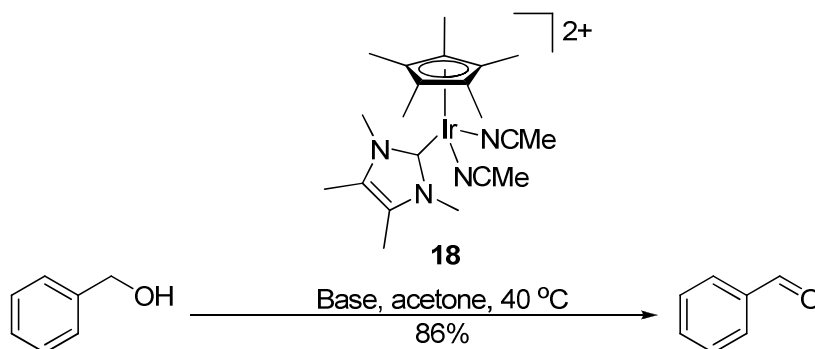
Noyori’s catalyst systems and variations thereof are undoubtedly been the most powerful and successful transfer hydrogenation methodologies to date. They have been shown to be impressively robust, displaying a broad substrate scope and excellent functional group tolerance. They also require low catalyst loadings at room temperature offering practical simplicity. A comprehensive review on asymmetric transfer hydrogenation is available from Wills and Palmer.<sup>54</sup>

Whilst the reduction of ketones has been much developed in the field of homogeneous transfer hydrogenation, the corresponding Oppenauer type oxidation of alcohols has remained fairly undeveloped. Ruthenium catalysts are generally applicable to the oxidation of secondary alcohols, however there are very few examples of oxidation of primary alcohols to aldehydes.<sup>55</sup> The lack of examples can be attributed to the incompatibility of many ruthenium complexes with the product aldehydes. Decarbonylation is also an obstacle, leading to catalyst deactivation via formation of a ruthenium *bis*-carbonyl complex.<sup>56</sup> For example, De Vries has reported the decarbonylation of cinnamaldehyde with  $\text{Ru}(\text{PPh}_3)_4\text{H}_2$ .<sup>57</sup> In addition, further reactions of the product aldehydes are common, for example formation of esters by reaction with the starting alcohols as demonstrated by Blum *et al.*<sup>36</sup>

Similarly, examples of iridium catalysed oxidations of alcohols *via* transfer hydrogenation are known, but again are relatively unknown in comparison with the vast amount of reduction chemistry reported. However, iridium complexes are shown to oxidise secondary and primary alcohols (albeit at a slower rate) but don’t exhibit any of the shortfalls found ruthenium systems. This allows iridium based systems to negate the problems experienced with the ruthenium systems. Probably the most significant results achieved are those by Yamaguchi, who has reported a cationic pentamethylcyclopentadienyl iridium *N*-heterocyclic carbene complex **18** which

catalyses the oxidation of both primary and secondary alcohols at a respectable rate under mild conditions.<sup>58, 59</sup> This is the most active iridium system known to date.

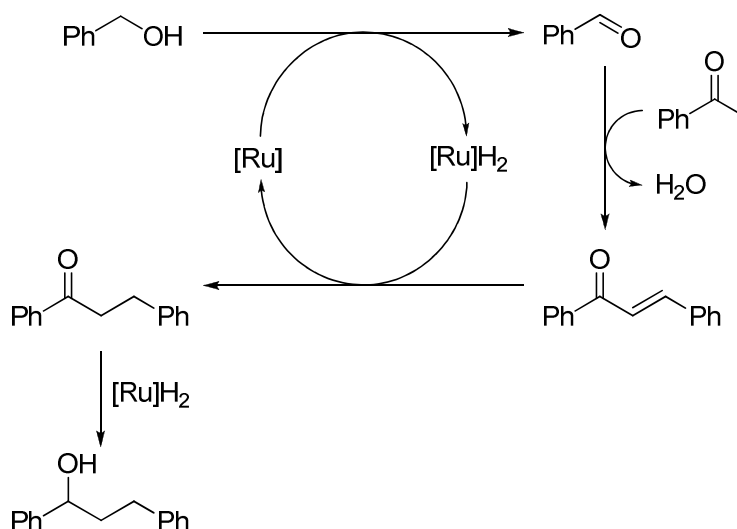
(Scheme 19)



**Scheme 19.** Yamaguchi's Oppenauer type oxidation with an Ir-NHC catalyst.

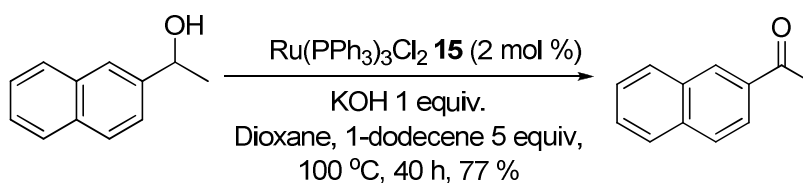
The reduction of olefins *via* homogeneous transfer hydrogenation has also remained undeveloped in comparison with the wealth of research reported on carbonyl groups. Nolan and co-workers have reported the best system, using an iridium complex to reduce a wide range of alkenes in excellent yields using 2-propanol as the hydrogen donor.<sup>60</sup> Crabtree has also reported a triazole-derived iridium(I) carbene catalyst to achieve reduction of alkenes.<sup>61</sup> Interestingly, these catalysts also exhibit wide substrate scope, with aldehydes, ketones and imines all being reduced. Ruthenium based systems for the reductions of olefins by transfer hydrogenation are rare. Blum<sup>35</sup> has utilised 2-propanol as a hydrogen donor in the reduction of the alkene bond in  $\alpha,\beta$ -unsaturated ketones selectively. More recently Cho<sup>62</sup> *et al* also used  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** to reduce ketones together with reduction of the olefin moiety *via* transfer hydrogenation after an aldol coupling reaction to produce the unexpected homologated alcohol product (Scheme 20).





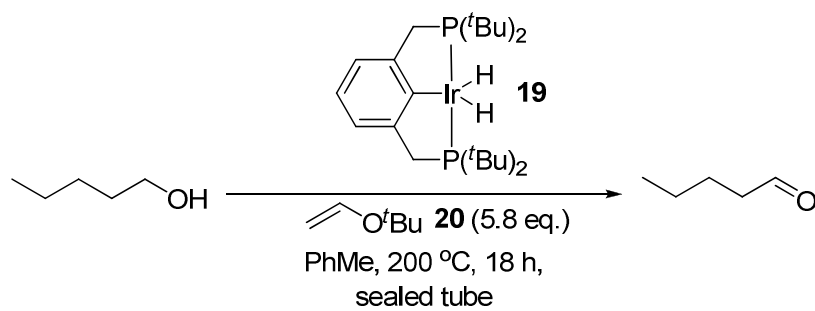
**Scheme 20.** Double reduction in a transfer hydrogenation reaction.

Cho has also utilised a simple alkene to facilitate the oxidation of secondary alcohols.<sup>63</sup> Using 1-dodecene as the hydrogen acceptor and using  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** as catalyst, secondary alcohols were oxidised in good yields (**Scheme 21**).



**Scheme 21.** An alkene as a hydrogen acceptor.

Despite these reports, selective oxidation of alcohols using olefins as hydrogen acceptors has seldom been reported. The most notable examples have been systems which have utilised iridium systems (*vide supra*). Jensen, has developed the most notable system which utilises a novel PCP “pincer” complex **19** for the dehydrogenation of alcohols using an electron-rich alkene (*tert*-butyl vinyl ether) **20** as the hydrogen acceptor. This method was applied to primary and secondary alcohols with equal success. The high yields of products and absence of side reactions prove attractive. However, forcing conditions and a relatively large excess of alkene acceptor detract slightly from this useful system (**Scheme 22**).<sup>64</sup>

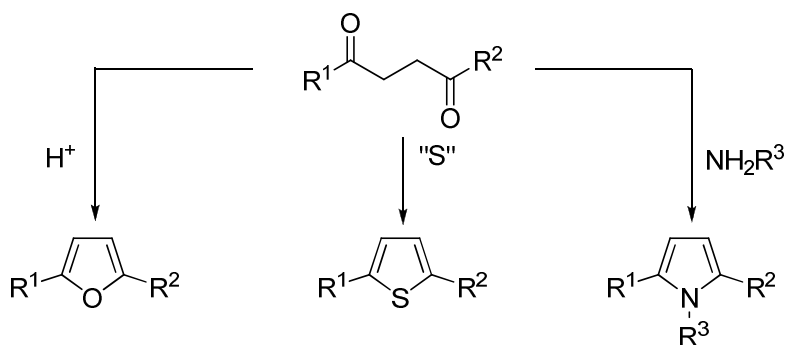


**Scheme 22.** Jensen's iridium catalysed alcohol oxidation.

### 1.3 Paal-Knorr Heterocycle Synthesis.

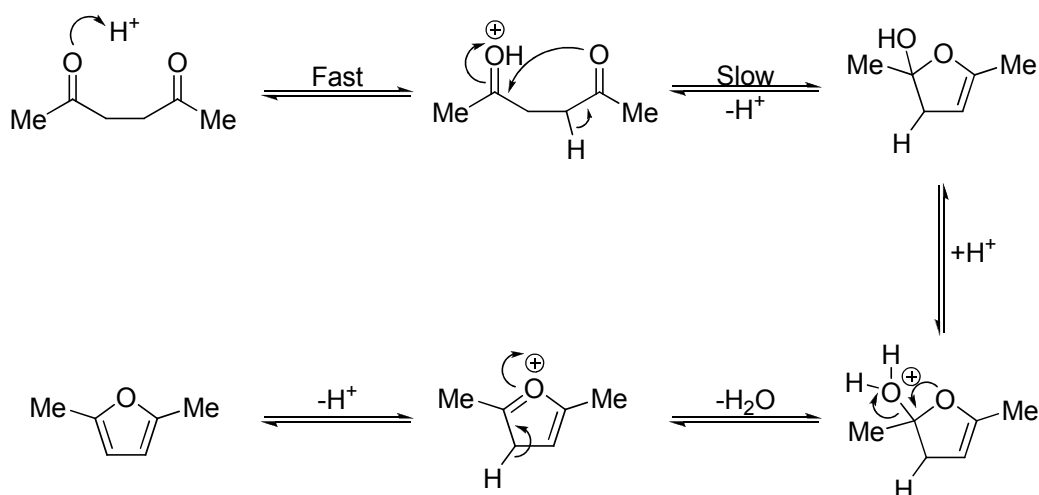
Furans and pyrroles are common heterocyclic compounds, broadly found in naturally occurring and biologically active compounds, as well as in material science. Furans and pyrroles represent important compounds, both as synthons and themselves as functionalised heterocycles. Approaches toward functionalised five-membered heterocycles can be divided into two groups: Functionalisation of a pre-existing heterocyclic core, and assembly of the ring from acyclic precursors. The latter route has greater potential for rapidly obtaining diversity in functionalised heterocycles. Within this group, the variations of Paal-Knorr synthesis have proven to be the most powerful method for the synthesis of furans and pyrroles.

In 1884 Paal and Knorr simultaneously reported that treatment of 1,4-diketones with strong mineral acids or with concentrated ammonia or ammonium acetate produced 2,5-disubstituted furans and pyrroles respectively.<sup>65,66</sup> The general features of the reaction is that any 1,4-dicarbonyl compounds and their surrogates can be used. However, mainly 1,4-diketones are utilised as 1,4-dialdehydes or keto aldehydes are generally less stable and lack any general methods for their preparation. Similarly, the use of a source of nucleophilic sulphur will result in thiophene derivatives (**Scheme 23**).<sup>67</sup>



**Scheme 23.** Paal-Knorr heterocycle synthesis.

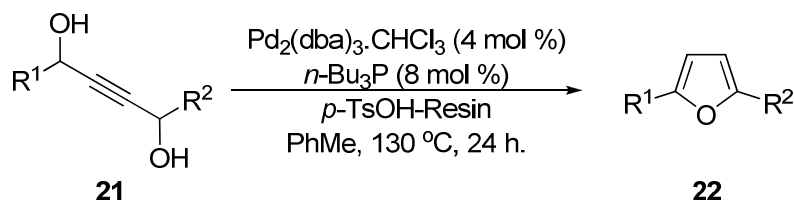
The exact mechanism of the Paal-Knorr furan reaction was the subject of much debate for more than a century since its conception. Amarnath and Amarnath published comprehensive NMR experimental data to show that the reaction proceeds via addition of the enol oxygen of one of the carbonyl groups to the other carbonyl group with subsequent elimination of water (**Scheme 24**).<sup>68</sup>



**Scheme 24.** Mechanism of the Paal-Knorr furan synthesis.

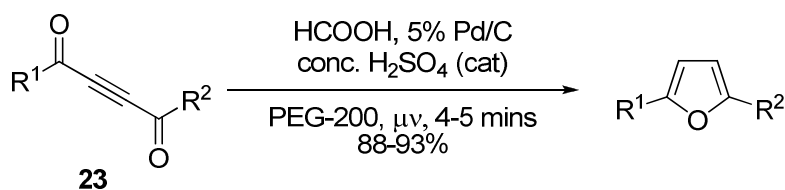
Research in the Paal-Knorr synthesis of furans has been sparse since its origin in 1884. Advances in the area have been limited to the use of various acid catalysts from strong mineral acids such as HCl to organic acids such as acetic acid, TFA and *p*-TsOH.<sup>69,70</sup> Lewis acids have also been utilised in the Paal-Knorr reaction such as zinc halides and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to afford cyclisation of 1,4-dicarbonyls.<sup>71</sup> However the limitations of the reaction such as accessibility to the various dicarbonyl compounds required and consequently functional group tolerance in both substrates and products have seen limited progress.

Most research on the Paal-Knorr reaction has focused on the synthesis of dicarbonyl surrogates to afford 2,5-disubstituted furans. This has led to more efficient and diverse reactions allowing a multitude of variously substituted furans to be synthesised in improved yields and with greater efficiency. These new processes help overcome the problems encountered in the traditional Paal-Knorr furan synthesis (*vide supra*).<sup>72-74</sup> Notable work in the area of 1,4-dicarbonyl surrogates was conducted by Lu *et al.* who used a palladium catalyst to isomerise 2-butyne-1,4-diol derivatives **21** to 1,4-dicarbonyl surrogates in the presence of acidic resin to afford the corresponding 2,5-disubstituted furans **22** (Scheme 25).<sup>75</sup> However, the high catalyst loading and temperature required as well as the requirement for a strong acid to be present to facilitate the cyclisation reaction still has limitations, but showed that improvement was possible by use of 1,4-dicarbonyl surrogates.



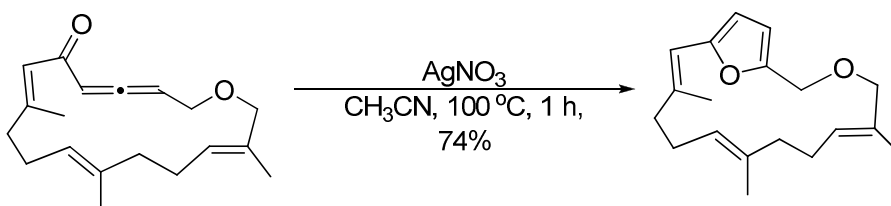
**Scheme 25.** Lu's 2-butyne-1,4-diol isomerisation-cyclisation reaction to afford furans.

Similarly Surya Prakash Rao<sup>76</sup> used 2-butyne-1,4-diones **23** as surrogates in the synthesis of furans. Reduction of the alkyne functionality using palladium on carbon with formic acid as the reductant was combined with sulphuric acid co-catalyst for the cyclisation under microwave conditions. A range of 2,5-furans was synthesised in good yield with reasonable functional group variation, in a one pot process (**Scheme 26**).



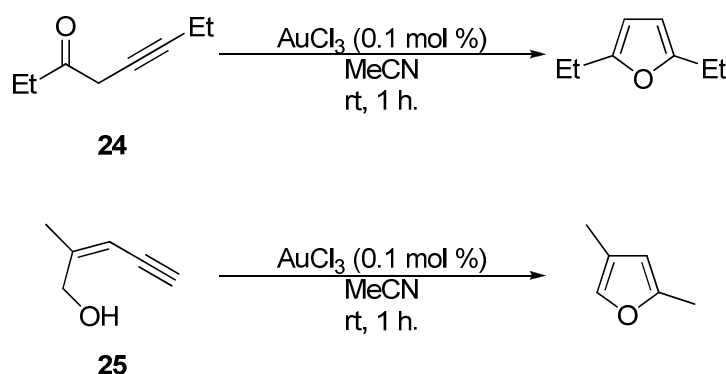
**Scheme 26.** Reduction of an alkynedione followed by cyclisation to furans.

A significant advance in the synthesis of furan has been the metal catalysed cycloisomerisation of alkyne and allene containing compounds. In 1990, Marshall<sup>77</sup> reported that allenones and allenals when treated with catalytic amounts of silver nitrate afforded furans as a result of a cycloisomerisation reaction (**Scheme 27**).



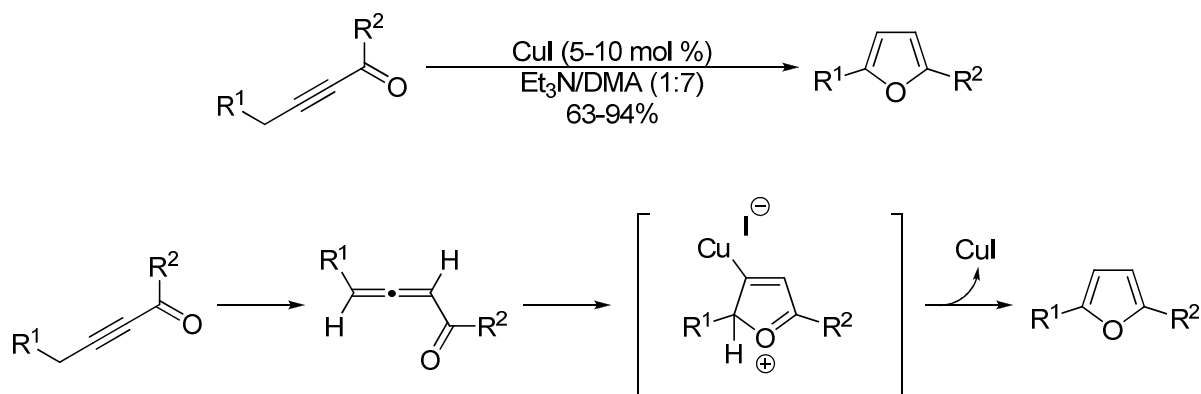
**Scheme 27.** Marshall's silver catalysed cycloisomerisation.

This work was improved upon in 1991 by Utimoto. Allenes prove to be difficult starting materials to prepare, requiring multistep synthesis, especially allenyl compounds containing sensitive functionalities. Utimoto utilised alkynones as starting materials in a palladium catalysed cycloisomerisation as a route to furans.<sup>78</sup> Alkynes proved to be much more attractive starting materials for cycloisomerisations due to their easy synthesis and compatibility with diverse functional groups. Subsequently, Marshall utilised a silver catalysed isomerisation of alkynyl allylic alcohols to afford variously substituted furans,<sup>79</sup> and Hashmi simplified this work in 2000. Using a gold catalyst, propynyl ketones **24** and (*Z*)-enynols **25** were cycloisomerised to afford variously substituted furans (**Scheme 28**).



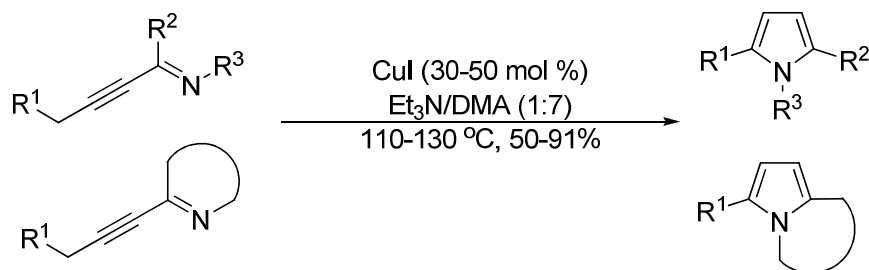
**Scheme 28.** Hashmi's gold catalysed cycloisomerisation.

Most of the late transition metals have been used to effect many similar cycloisomerisations. Palladium and ruthenium<sup>80,81</sup> however prove limited due to the high temperatures required to afford cyclisation. Rhodium, silver and particularly gold have proven to be the most successful catalysts to date.<sup>82</sup> Gold based catalysts are highly effective systems, with reactions proceeding at room temperature and below with minimal catalyst loadings. More recently, Gevorgyan has utilised cheaper and simpler copper catalysts combined with an amine base to cycloisomerise alkynones to furans. The reaction is believed to proceed through the intermediacy of an allenyl isomer, which then under-goes cyclisation (**Scheme 29**).<sup>83</sup>



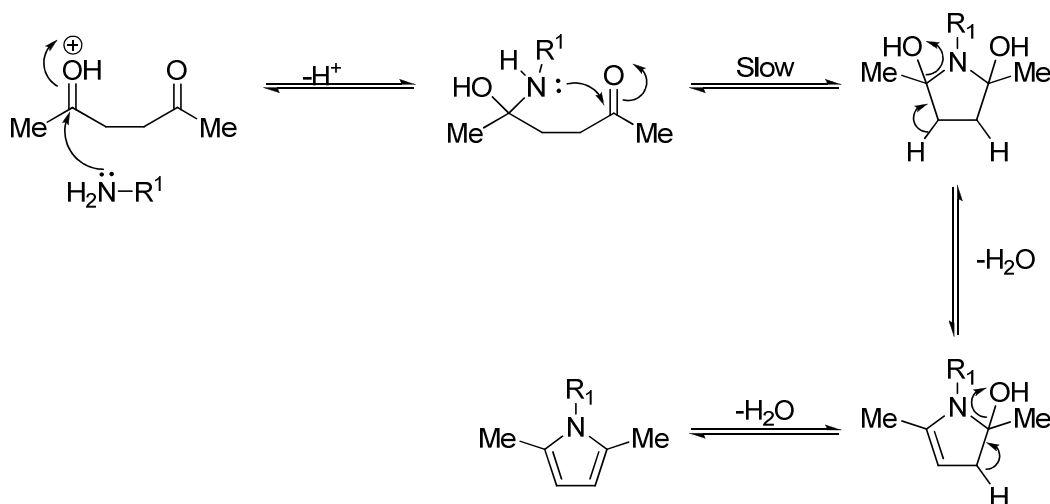
**Scheme 29.** Copper catalysed furan formation.

Gevorgyan has also applied this methodology in the synthesis of pyrroles. Replacing the alkynone with alkynylimines a copper catalysed cycloisomerisation has allowed formation of 2,5 and 2,5-*N*-substituted pyrroles as well as fused bicyclic pyrroles. (**Scheme 30**)<sup>84</sup>



**Scheme 30.** Gevorgyan's copper catalysed pyrrole synthesis

Very similar in a nature to the Paal-Knorr furan synthesis, pyrroles are synthesised from 1,4-dicarbonyl compounds and an excess of amine or ammonia. Virtually any amine and be used from aliphatic primary amines, both electron-rich and electron-poor aromatic amines and heterocyclic amines (e.g. aminopyridines).<sup>70</sup> Amarnath and Amarnath<sup>85</sup> again carried out extensive NMR studies to determine the reaction mechanism of the Paal-Knorr pyrrole synthesis (**Scheme 31**). Similarly to the mechanism for furan synthesis, the cyclisation step was found to be the rate determining step.

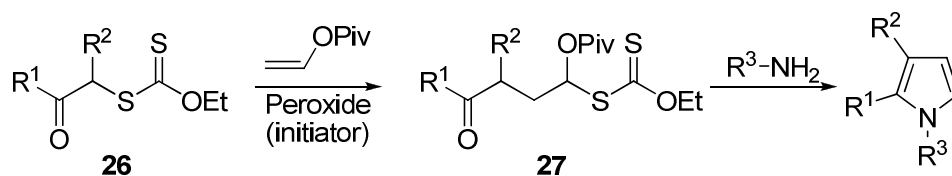


**Scheme 31.** Mechanism of the Paal-Knorr pyrrole synthesis.

Like the Paal-Knorr furan reaction, the majority of research was focused in overcoming the traditional problems associated with the reaction, such as availability of 1,4-dicarbonyl compounds and functional group sensitivity and compatibility. The use of dicarbonyl surrogates and metal catalysed cycloisomerisations, as well as multicomponent reactions have dominated the research in this area.

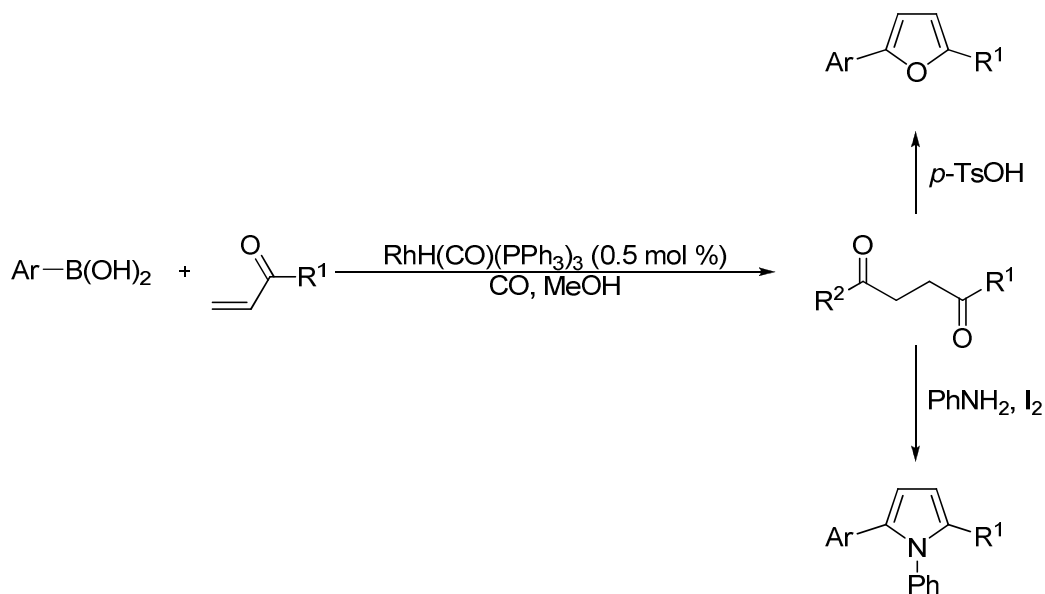
Taddei *et al.* applied a homologation of  $\beta$ -ketoester with an aldehyde followed by oxidation to allow a new route to various 1,4-dicarbonyl compounds, which in turn were cyclised in the presence of amine to cyclise with the Paal-Knorr procedure under microwave conditions to afford variously substituted pyrroles. As expected, replacement of stoichiometric amine with an acid catalyst afforded furans.<sup>86</sup> In a novel approach, Azizian<sup>87</sup> used 4-hydroxyproline as an already cyclised surrogate. Upon treatment with various ketones in DMSO under microwave conditions in the presence of montmorillonite K10, various *N*-substituted pyrroles were synthesised. This method proved a practical way around the difficulty posed by the synthesis of 1,4-dialdehydes. Zard *et al.*<sup>88</sup> used a radical addition of  $\alpha$ -xanthyl ketones **26** to pivalate to give adducts **27** that are synthetically equivalent of 1,4-ketoaldehydes. Further treatment with ammonia or primary amines lead to the corresponding pyrroles (**Scheme 32**).





**Scheme 32.** A novel route to 1,4-ketoaldehyde surrogates.

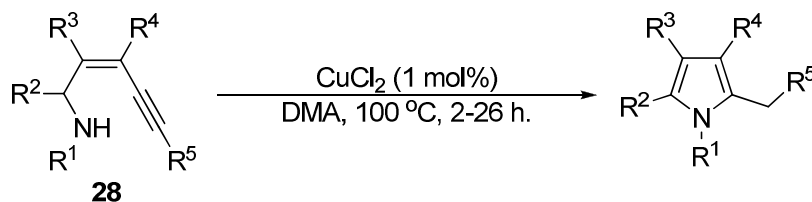
More recently, Mortreux has reported an elegant one pot route to furans and pyrroles using a rhodium catalysed 1,4-carbonylative addition of arylboronic acids to vinylketones to synthesise 1,4-dicarbonyls. The dicarbonyls are then cyclised *in situ* to afford the corresponding furan and pyrrole derivatives (**Scheme 33**).<sup>89</sup>



**Scheme 33.** Mortreux's route to 1,4-dicarbonyls with cyclisation to pyrroles and furans

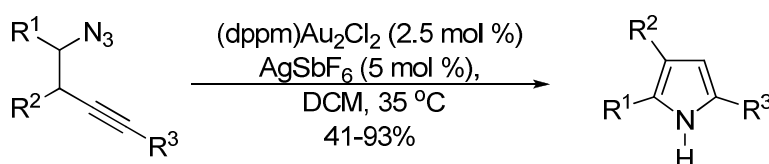
As seen with furans (*vide supra*), transition metal catalysts have been employed as a route to pyrroles. Pyrroles have been synthesised using titanium, gold, silver, palladium, copper and zinc salts and complexes to afford pyrroles of varying substitution patterns and degrees of complexity. Again, these transition metal catalysed routes overcome the barriers and constraints normally encountered with the classical Paal-Knorr route to pyrroles. By modification of alkynic and allenic substrates witnessed in the metal catalysed synthesis of furans, pyrroles can be obtained.

The *exo*-cyclisation of *Z*-enamines **28**, analogous to *Z*-enynols (*vide supra*) was reported by Gabriele in 2001, using a palladium catalyst.<sup>90</sup> However this early system was flawed with limited substrate scope. However in 2003 Gabriele reported a much improved system that utilised copper(II) chloride as catalyst (**Scheme 34**). Palladium chloride was also found to be a useful catalyst in the system depending on substitution patterns on the pyrrole required.<sup>91</sup>



**Scheme 34.** Gabriele's pyrrole synthesis from *Z*-enamines.

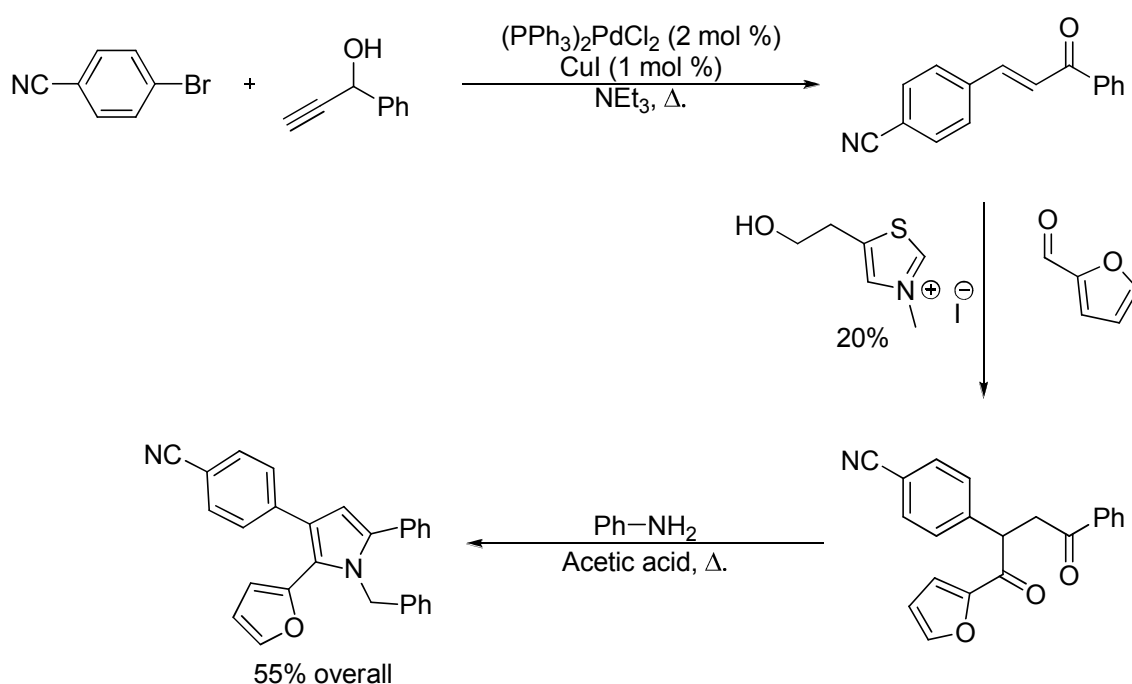
With allenes being inherently difficult to prepare and manipulate, alkynic substrates have been the main focus in the development of cycloisomerisation routes to pyrroles. Dake has used  $\beta$ -alkyneones as starting materials when combined with an equivalence of primary amines using silver(I) trifluoromethanesulfonate (AgOTf) or cationic gold(I) complexes as the catalysts. The reaction proceeds via *in situ* formation of the  $\beta$ -alkynimines which then cyclise around to the metal activated alkyne.<sup>92</sup> Toste *et al.* have also utilised a gold(I) catalyst to achieve an intermolecular Schmidt reaction under mild conditions with good functional group tolerance (**Scheme 35**).<sup>93</sup>



**Scheme 35.** Gold catalysed intermolecular Schmidt reaction.

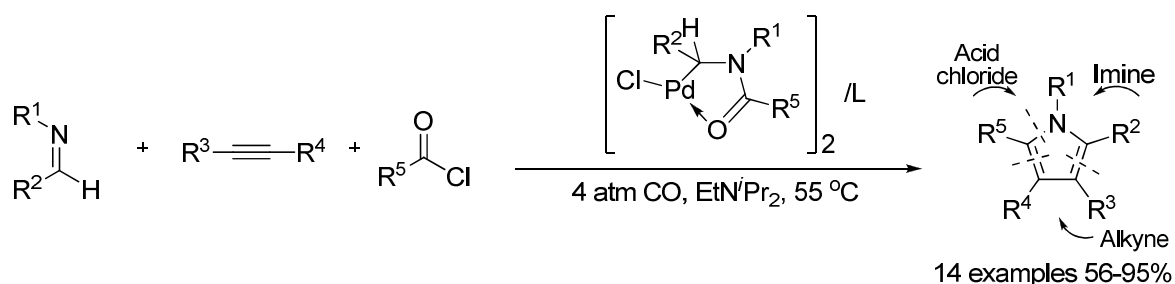
In 2004, Odom improved even further on the use of alkynes in the synthesis of pyrroles. Using titanium based catalysts Odom synthesised pyrroles *via* the hydroamination of 1,4 and 1,5-diynes with primary amines to afford imino-alkynes.<sup>94</sup> These imino-alkynes can then undergo 5-*endo* and 5-*exo*-cyclisations (depending on the starting materials used) to afford the pyrrole products in a one pot reaction. This approach further simplifies the use of alkynes for pyrrole synthesis.

Novel routes using 1,4-dicarbonyl surrogate compounds coupled with a metal catalyst have overcome the barriers of the traditional Paal-Knorr reaction. In the interest of developing new greener processes, multi-component and one pot reactions have become valuable in the synthesis of furans and pyrroles. 1,2,3,5-Tetrasubstituted pyrroles have been synthesised by Müller *et al.* in a one pot, three step, four component process by a coupling-isomerisation-Stetter reaction-Paal-Knorr sequence of an electron poor heteroaryl halide, a terminal propargylic alcohol, an aldehyde and a primary amine. The initial coupling step being catalysed by a palladium based system (**Scheme 36**).<sup>95</sup>



**Scheme 36.** Müller's one-pot route to pyrroles.

Arndtsen reported a one pot direct synthesis of pyrroles using a palladium catalysed multicomponent coupling of alkynes, imines and acid chlorides, further improving the multi-component, one-pot strategy to pyrroles. Arndsten exploited the ability of alkynes to undergo 1,3-dipolar cycloaddition to 1,3-oxazolium-5-oxides (Münchones) to form pyrroles.<sup>96,97</sup> While Arndtsen had previously reported the synthesis of Münchones by the palladium catalysed coupling of imines with acid chlorides and carbon monoxide,<sup>98</sup> addition of alkynes showed to be a useful way to construct pyrroles (**Scheme 37**).<sup>97</sup>

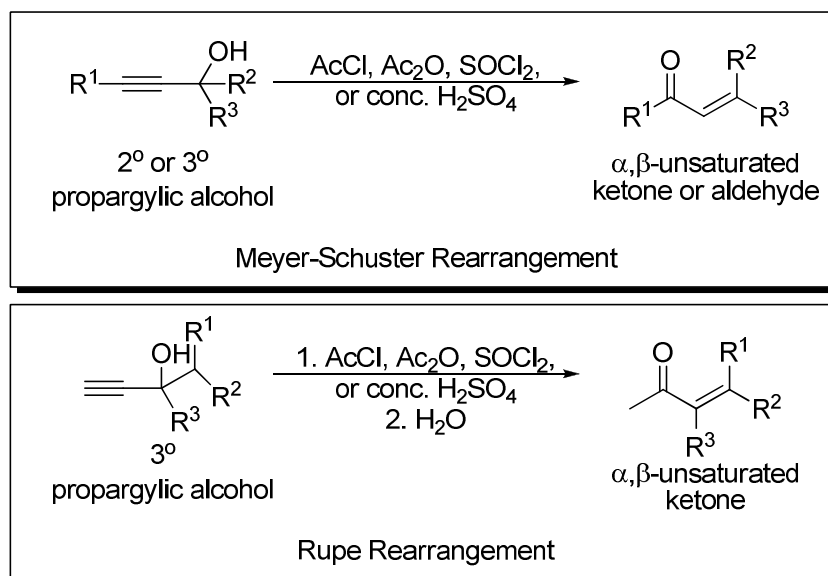


**Scheme 37.** Three component approach to pyrroles from Münchones.

Since Paal and Knorr conceived the reaction of 1,4-dicarbonyl compounds with acids and amines, much research has been conducted in order to improve on the synthesis of these heterocycles and to overcome the synthetic barriers present in the classical reaction. There have been many original and efficient ways to obtain 1,4-dicarbonyl surrogates which can then be cyclised in order to afford the requisite furan and pyrrole. However, it is with metal catalysts combined with alkynic and allenic substrates and the development of multicomponent reactions that have shown to be highly efficient routes to furans and pyrroles. These reactions improve functional diversity and chemoselectivity. This area is likely to provide a large amount of exciting new research in the future.

#### 1.4 Meyer-Schuster-Rupe Rearrangements and Redox Isomerisations.

In 1922, K. H. Meyer and K. Schuster reported that the attempted conversion of 1,1,3-triphenyl-2-propyn-1-ol into the corresponding ethyl ether with concentrated sulphuric acid unexpectedly gave rise to the  $\alpha,\beta$ -unsaturated ketone, 1,1,3-triphenyl propeneone.<sup>99</sup> The authors also demonstrated that other reagents such as acetic anhydride and acetyl chloride also facilitated the same reaction. A few years later Rupe and co-workers were investigating this acid catalysed rearrangement of a large number of propargylic alcohols and found a similar rearrangement product. (**Scheme 38**)<sup>100</sup>



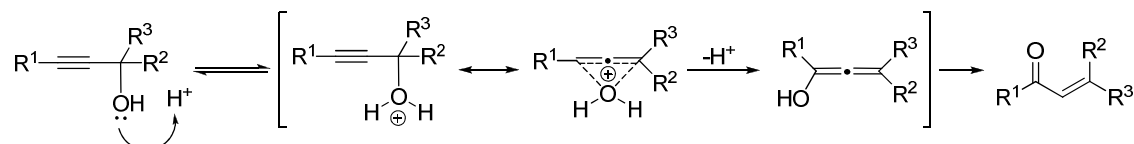
**Scheme 38.** General Meyer-Schuster and Rupe rearrangements.

The acid catalysed isomerisation of secondary and tertiary propargylic alcohols *via* a [1,3]-shift of the hydroxyl group, to the corresponding  $\alpha,\beta$ -unsaturated carbonyl is known as the Meyer-Schuster rearrangement. When the substrate contains a terminal alkyne the product is the,  $\alpha,\beta$ -unsaturated aldehyde, whereas with a disubstituted alkyne the product will be the  $\alpha,\beta$ -unsaturated ketone. The substrates are generally secondary and tertiary propargylic alcohols but without an  $\alpha$ -hydrogen so that the initial propargylic cation can isomerise to the allenyl cation, which provides the product carbonyl compound. In both reactions the rearrangement can be catalysed by both protic and Lewis acids. The acid catalysed isomerisation of tertiary alcohols *via* the [1,3]-shift of the hydroxyl group to yield the corresponding  $\alpha,\beta$ -unsaturated ketone is known as the Rupe rearrangement. The product of the Rupe rearrangement is always an  $\alpha,\beta$ -unsaturated ketone, regardless of the substitution present on the triple bond. Similar to

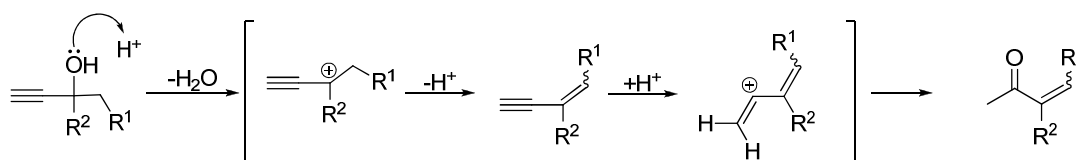
the Meyer-Schuster reaction there cannot be any  $\alpha$ -hydrogens present next to the alcohol.

The mechanism of these transformations, as with many of the classical reactions was the subject of much debate. However, the work of Schiavelli<sup>101</sup> and Hennon<sup>102</sup> resulted in the generally accepted mechanisms for the reactions shown in (**Scheme 39**).

Meyer-Schuster rearrangement



Rupe Rearrangement



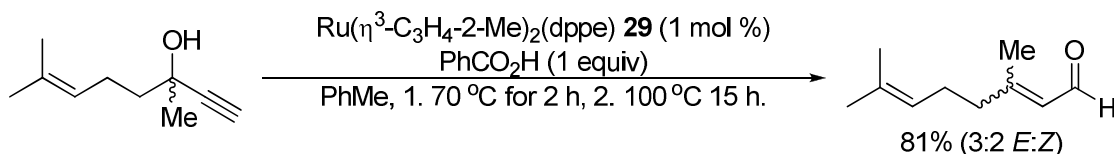
**Scheme 39.** Mechanisms for the Meyer-Schuster and Rupe rearrangements

The disadvantages of these two rearrangements are the obvious use of functionalities sensitive to acid conditions which limits substrate scope. Certain substrates can give rise to both the Meyer-Schuster and Rupe rearranged products, along with low yields of product, especially when the products are aldehydes which undergo self-condensation or are readily oxidised under the reaction conditions.

Strong acidic conditions and elevated temperatures often give rise to non-regioselective transformations and seriously limit the applicability of these rearrangements. Although more selective catalyst systems based on transition metal oxides have been developed, harsh conditions are still required.<sup>103,104</sup>

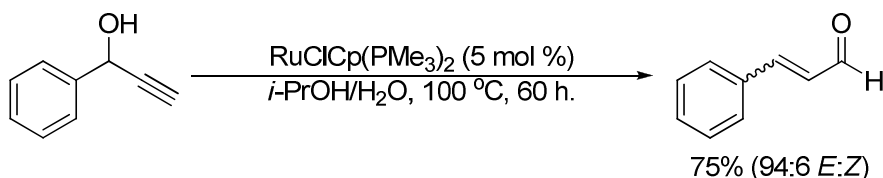
With ruthenium's ability to activate carbon-carbon triple bonds many new reactions have been developed to improve on the Meyer-Schuster and Rupe rearrangements under milder conditions. Pioneering work in the field was conducted by Dixneuf and co-workers<sup>105</sup> who used a bis(allyl)ruthenium(II) complex **29** with an equivalent of benzoic acid to achieve the selective Meyer-Schuster isomerisation of several tertiary terminal alkynols. The resulting  $\alpha,\beta$ -unsaturated aldehyde products were isolated in moderate to

good yields. However, no control over the double bond geometry was achieved (**Scheme 40**).



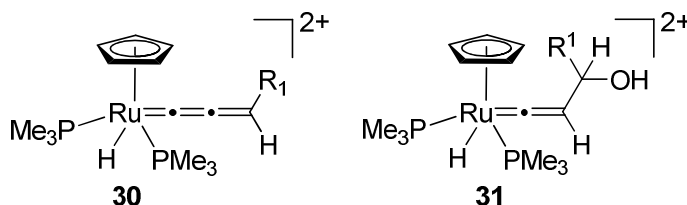
**Scheme 40.** Dixneuf's ruthenium catalysed Meyer-Schuster isomerisation.

A more direct and selective transformation has been accomplished by Wakatsuki and co-workers employing  $[\text{RuCl}(\eta^5\text{-Cp})(\text{PMe}_3)_2]$  as a catalyst.<sup>106</sup> Wakatsuki isolated a variety of enals in high yields from monosubstituted propargylic alcohols in propan-2-ol/water (3:1) mixture at 100 °C (**Scheme 41**).



**Scheme 41.** Ruthenium catalysed Meyer-Schuster isomerisation.

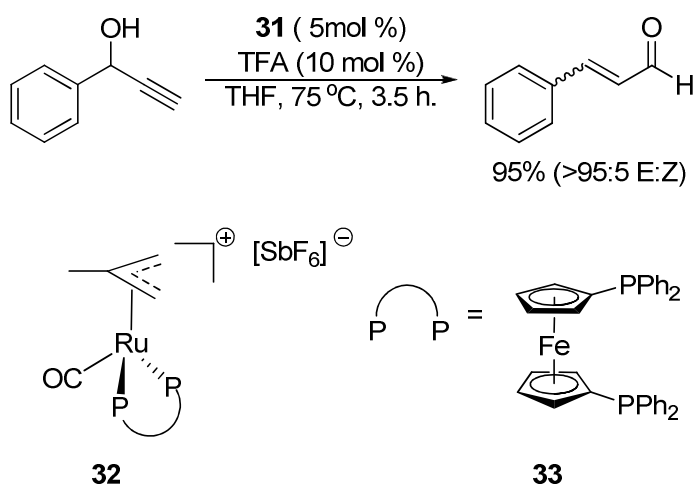
An anti-Markovnikov hydration of the alkyne moiety with simultaneous dehydration of the hydroxyl group had been proposed by the authors as the possible reaction pathway. Moreover they have suggested that nucleophilic addition of water to the electrophilic  $\alpha$ -carbon of hydridoruthenium(IV)-allenylidene **30** or (hydroxymethyl)vinylidene **31**, could be involved in the hydration step (**Scheme 42**).<sup>107,108</sup>



**Scheme 42.** Proposed catalytic intermediates in Wakatsuki's ruthenium catalysed Meyer-Schuster isomerisation

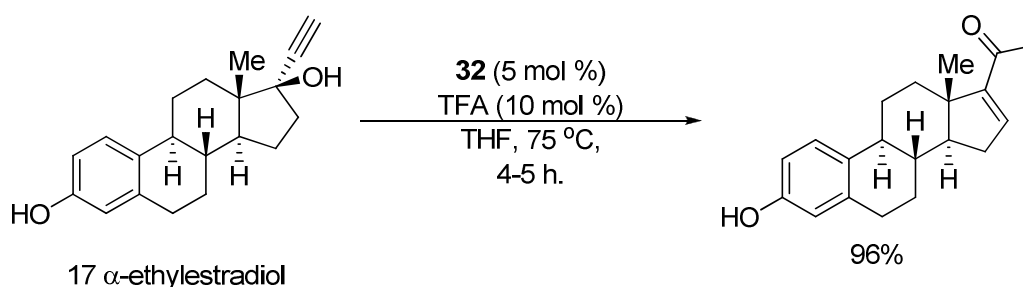
Cadierno *et al.* further improved on these systems in 2004 but utilising a 16-electron cationic ruthenium species.<sup>109</sup> An  $(\eta^3\text{-allyl})\text{ruthenium(II)}$  derivative when combined

with 1,1'-bis(diphenylphosphino)ferrocene (dppf) **33** to form complex **32**, with catalytic amounts of trifluoroacetic acid (TFA) in refluxing THF allowed a variety of enals to be synthesised in greater than 90% yield in reaction times ranging from 12 minutes to 3.5 hours. A remarkable feature of the catalyst used is the complete control of the double bond stereochemistry. By using secondary propargylic alcohols the resulting enals were formed almost exclusively as the thermodynamically more stable *E*-isomers (**Scheme 43**).<sup>110</sup>



**Scheme 43.** Cadierno's ruthenium catalysed Meyer-Schuster rearrangement.

Cadierno has also demonstrated the usefulness of complex **32**, in reporting the first Rupe type isomerisation catalysed by ruthenium based complexes. This catalyst was applied to the reaction of hormonal steroid 17  $\alpha$ -ethylestradiol using in a Rupe rearrangement showing the versatility of this catalyst (**Scheme 44**).<sup>110</sup>



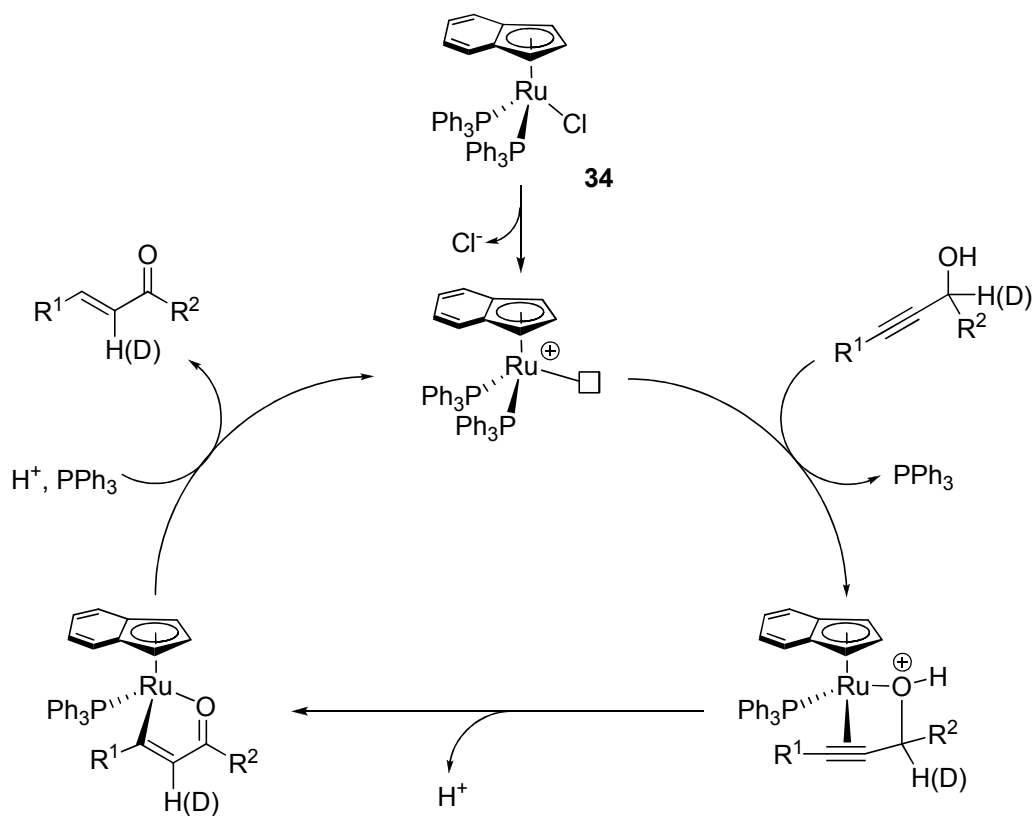
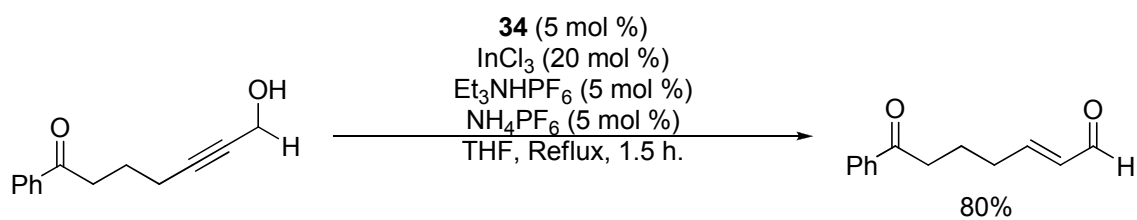
**Scheme 44.** The first example of a ruthenium catalysed Rupe rearrangement.

These complexes presented by Dixneuf, Wakatsuki and Cadierno represent the usefulness of ruthenium catalysed Meyer-Schuster and Rupe rearrangements



overcoming the inherent barriers present in the traditional reactions, and metal catalysed rearrangements of various propargylic alcohols is still an exciting area of research.<sup>111,112</sup> In addition to the classical Meyer-Schuster rearrangements, propargylic alcohols can also undergo redox-type isomerisations, i.e. not involving the transposition of the oxygen atom. To date only ruthenium complexes have been able to promote such a transformation efficiently.

Following seminal studies by Ma and Lu<sup>113</sup> using  $\text{RuCl}_2(\text{PPh}_3)_3$  **15** as a catalyst Trost and Livingston identified over a decade ago the highly efficient catalytic system of the indenyl-ruthenium(II) complex **34** combined with indium trichloride and triethylammonium hexafluorophosphate.<sup>114</sup> Enals were synthesised chemo and stereoselectively (*E*-isomers) in yields ranging from 67-88%, after only 90 minutes in refluxing THF. The reaction with internal propargylic alcohols to produce enones proceeded more slowly but still gave the products in excellent yields. Remarkably, this methodology also tolerates the presence of a range of functional groups including carbonyls, esters, alcohols, alkynes and alkenes. The role played by the Lewis acid, indium trichloride is important in this catalytic transformation as its absence led to very low conversion ca. 30%. Using deuterium labelling studies the mechanism for this redox isomerisation has been proposed as shown in (**Scheme 45**).

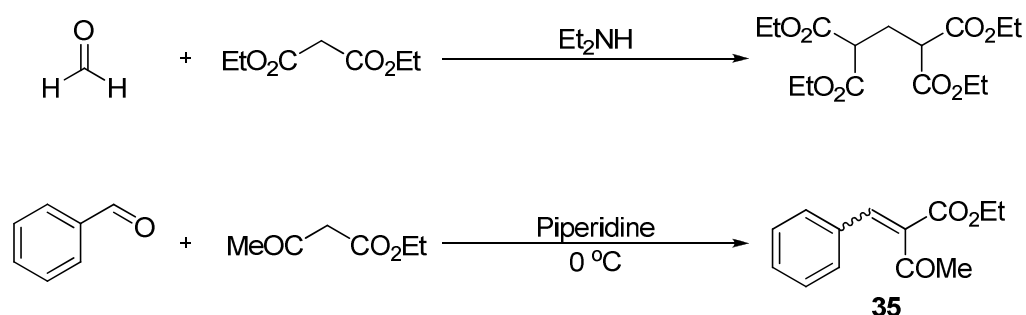


**Scheme 45.** Ruthenium catalysed redox isomerisation and mechanism.

(□-Indicates a vacant site)

## 1.5 Knoevenagel Condensation

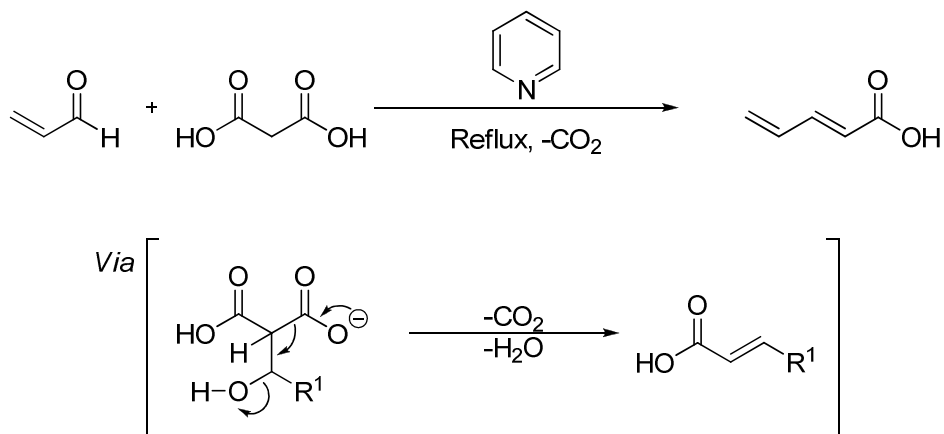
The Knoevenagel condensation is a fundamental reaction in which aldehydes and ketones react with activated methylene compounds in the presence of a weak base to afford  $\alpha,\beta$ -unsaturated dicarbonyl compounds with liberation of water. Emil Knoevenagel reported in 1894 the diethylamine catalysed condensation of diethyl malonate with formaldehyde in which he isolated the *bis* adduct.<sup>115</sup> Two years later Knoevenagel carried out the reaction of benzaldehyde with ethyl acetoacetate using piperidine as the catalyst and obtained ethyl benzylidene acetoacetate **35** as the sole product (**Scheme 46**).<sup>116</sup>



**Scheme 46.** Knoevenagel condensation

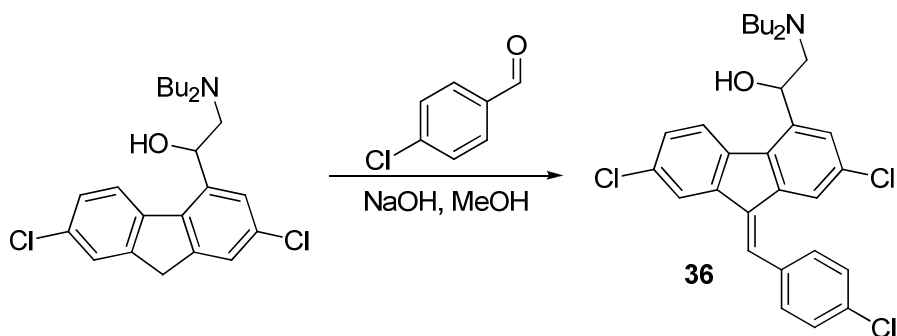
Classical reaction conditions involve the reaction of an aldehyde (ketones can also be used but react much more slowly) with an activated methylene compound in a polar aprotic solvent such as DMF in the presence of a catalyst, usually a primary, secondary or tertiary amine or their ammonium salts. Activated methylene compounds need to contain two electron withdrawing groups and typical examples include malonic esters and acids, malononitrile, and acetyl acetone. The two electron withdrawing groups can also be different such as in acetoacetic esters and cyano acetic acid.<sup>117</sup> Alternative catalysts have included group 1 fluoride salts<sup>118,119</sup> titanium tetrachloride coupled with a tertiary amine (The Lehnert modification)<sup>120-122</sup> and to heterogeneous methods such as dry alumina (Foucaud modification),<sup>123</sup> montmorillonite and xonolite treated with potassium *tert*-butoxide and zinc acetate.<sup>124</sup> Polymer supported amine catalysts<sup>125</sup> have been used to good effect in providing solutions to the problems encountered in the traditional Knoevenagel condensation. Similarly, other useful modifications such as microwave irradiation,<sup>126</sup> ultrasound techniques,<sup>127</sup> solvent free conditions<sup>128</sup> and ionic liquids<sup>129,130</sup> have all been utilised.

In 1902, Doebner found that when conducting the Knoevenagel condensation with carboxylic acid containing activated methylenes in refluxing pyridine that concerted decarboxylation and elimination occurs. This became known as the Doebner modification (**Scheme 50**).<sup>131</sup>



**Scheme 50.** The Doebner modification of the Knoevenagel condensation.

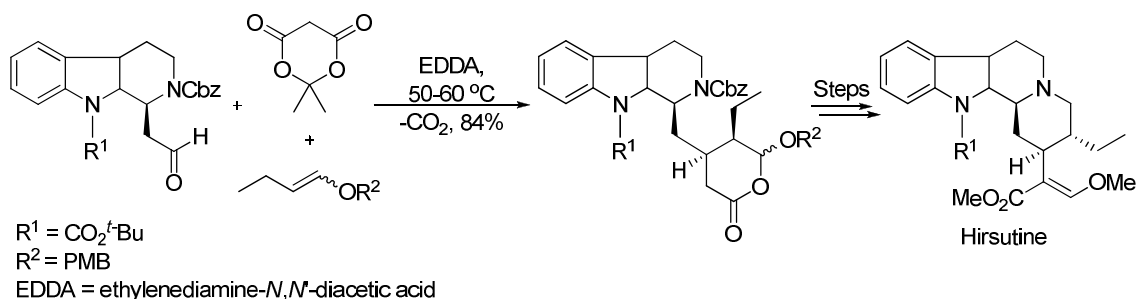
Synthetically, the Knoevenagel reaction is very useful. The Hantzsch pyridine synthesis, the Gewald reaction and the Feist-Bénary furan synthesis all contain a Knoevenagel reaction step. The Knoevenagel reaction has been used as the key step in the synthesis of antimalarial drug lumefantrine **36** (a component of Coartem)<sup>132</sup> (**Scheme 51**).



**Scheme 51.** Knoevenagel condensation in the synthesis of an anti-malarial drug.

The Knoevenagel condensation has also been used to great effect in tandem and domino reactions. A superb example is the work of Tietze and co-workers in the enantioselective total synthesis of hirsutine, an anti-influenza A alkaloid. The Knoevenagel condensation was carried out using Meldrum's acid and an enantiopure aldehyde in the presence of ethylenediamine acetate. The resulting highly reactive 1-oxa-1,3-butadiene underwent a hetero-Diels-Alder reaction *in situ* with 4-

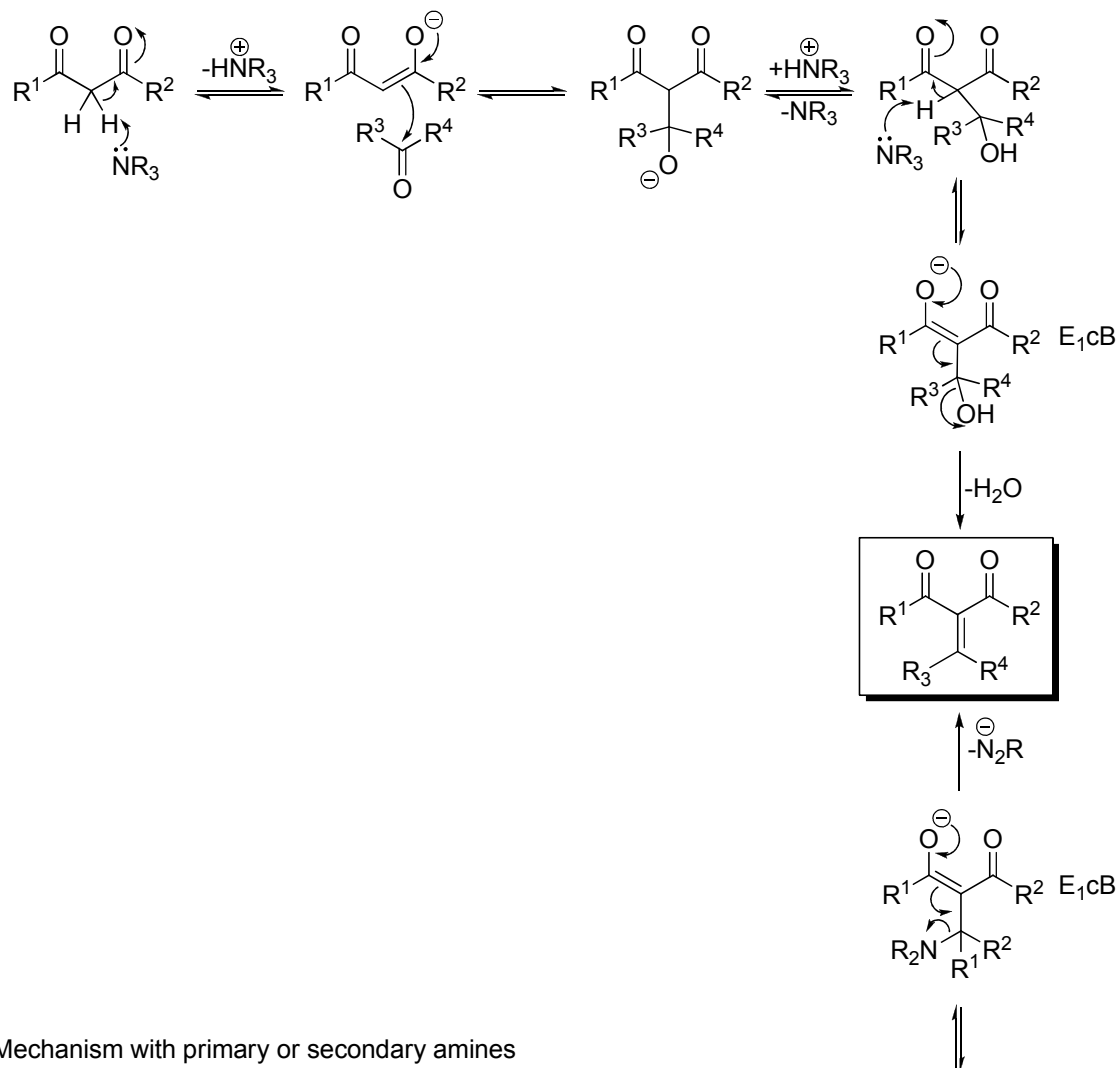
methoxybenzyl butenyl ether. The product exhibited a 1,3-asymmetric induction greater than 20:1<sup>133</sup> (**Scheme 52**). There are comprehensive reviews on the use of a Knoevenagel condensation in Tandem and domino reactions available.<sup>1,134</sup>



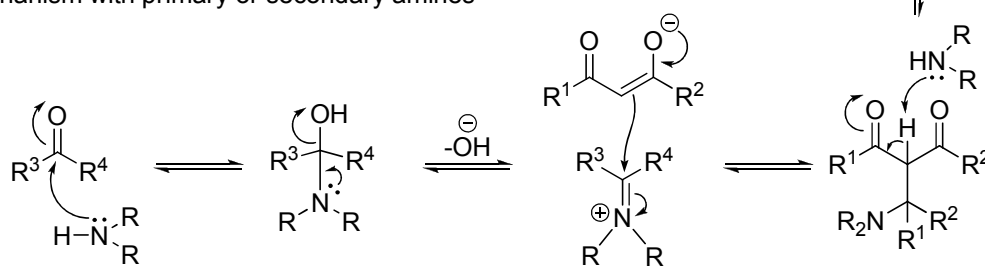
**Scheme 52.** Tietze's synthesis of hirsutine using a Knoevenagel-hetero-Diels-Alder tandem reaction as the key step.

The Knoevenagel condensation is a base catalysed aldol type reaction, and the exact mechanism depends on the substrates and catalyst used. There are two generally accepted mechanisms for the basic Knoevenagel reaction. The first is the Hann-Lapworth mechanism. Proposed in 1904, the mechanism concerns the use of tertiary amines as the catalyst. When tertiary amines are used as catalysts, the formation of a  $\beta$ -hydroxydicarbonyl intermediate is expected.<sup>135</sup> When primary or secondary amines are used as catalysts, the aldehyde and amine condense to form the iminium salt that then reacts with the enolate. Finally, a 1,2-elimination gives rise to the desired  $\alpha,\beta$ -unsaturated dicarbonyl or related compounds<sup>136, 137</sup> (**Scheme 53**). The final product may undergo a Michael addition with the excess enolate to give the *bis* adduct.

Hann-Lapworth mechanism with tertiary amines



Mechanism with primary or secondary amines



**Scheme 53.** Mechanisms involved in the Knoevenagel condensation

**1.6 References**

1. Tietze, L. F.; Modi, A., *Med Res. Rev.*, **2000**, 20, 304.
2. Tietze, L. F., *Chem. Rev.*, **1996**, 96, 115.
3. Waldmann, H., *Organic synthesis highlights*, **1995**, 2, 193.
4. Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., *Chem. Rev.*, **2005**, 105, 1001.
5. Robinson, R., *J. Chem. Soc.*, **1917**, 762.
6. Corey, E. J.; Virgil, S. C.; Sarshar, S., *J. Am Chem. Soc.*, **1991**, 113, 8171.
7. Nicolaou, K. C.; Montagnon, T.; Snyder, S. A., *Chem Commun.*, **2003**, 551.
8. Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C., *J. Am. Chem. Soc.*, **1986**, 108, 856.
9. Molander, G. A.; Harris, C. R., *Chem. Rev.*, **1996**, 96, 307.
10. Poli, G.; Giambastiani, G.; Heumann, A., *Tetrahedron* **2000**, 56, 5959.
11. de Meijere, A.; Brase, S., *J. Organomet. Chem.*, **1999**, 576, 88.
12. Trnka, T. M.; Grubbs, R. H., *Acc. Chem. Res.*, **2001**, 34, 18.
13. McLain, S. J.; Arthur, S. D.; Hauptman, E.; Feldman, J.; Nugent, L. K.; Johnson, S.; Mecking, S.; Brookhart, M., *Polym. Mater. Sci. Eng.*, **1997**, 76, 246.
14. Drouin, S. D.; Yap, G. P. A.; Fogg, D. E., *Inorg. Chem.*, **2000**, 39, 5412.
15. Louie, J.; Bielawski, C. W.; Grubbs, R. H., *J. Am. Chem. Soc.*, **2001**, 123, 11312.
16. Meerwein, H.; Schmidt, R., *Liebigs. Ann. Chem* **1925**, 444, 221.
17. Verley, A., *Bull. Soc. Chim. Fr.*, **1925**, 37, 537
18. Ponndorf, W., *Angew. Chem.*, **1926**, 39, 138.
19. Oppenauer, R. V., *Recl. Trav. Chim. Pay B.*, **1937**, 56.
20. Degraauw, C. F.; Peters, J. A.; Vanbekkum, H.; Huskens, J., *Synthesis.*, **1994**, 1007.
21. Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, I.; Maruoka, K., *Synthesis.*, **2002**, 279.
22. Ooi, T.; Otsuka, H.; Miura, T.; Ichikawa, H.; Maruoka, K., *Org. Lett.*, **2002**, 4, 2669.
23. Graves, C. R.; Zeng, B. S.; Nguyen, S. T., *J. Am. Chem. Soc.*, **2006**, 128, 12596.
24. Knoevenagel, E.; Bergdolt, B., *Chem. Ber.*, **1903**, 36, 2596.
25. Wieland, H., *Chem. Ber.*, **1912**, 45, 484
26. Pavlol, G. S.; Zelinski, N. D., *Chem. Ber.*, **1933**, 68, 1420
27. Corson, B. B.; Ipatieff, V. N., *J. Am. Chem. Soc.*, **1939**, 51, 1056.

28. Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D., *Chem. Rev.*, **1985**, 85, 129.
29. Linstead, R. P.; Braude, E. A.; Mitchell, P. W. D.; Wooldridge, K. R. H.; Jackman, L. M., *Nature.*, **1952**, 169, 100.
30. Gottfried, B.; Gottfried, T. J., *Chem. Rev.*, **1974**, 74, 567.
31. Wilkinson, G.; Jardine, F. H.; Osborn, J. A.; Young, G. F., *Chem. Ind. (London)* **1965**.
32. Henbest, H. B.; Trocha-Grimshaw, J., *Chem. Commun.*, **1967**, 544.
33. Le Page, M. D.; James, B. R., *Chem. Commun.*, **2000**, 1647.
34. Tatsumi, T.; Kizawa, K.; Tominaga, H., *Chem. Lett.*, **1977**, 191.
35. Sasson, Y.; Blum, J., *J. Org. Chem.*, **1975**, 40, 1887.
36. Shvo, Y.; Blum, Y.; Reshef, D.; Menzin, M., *J. Organomet. Chem.*, **1982**, 226, C21.
37. Murahashi, S. I.; Ito, K. I.; Naota, T.; Maeda, Y., *Tetrahedron Lett.*, **1981**, 22, 5327.
38. Murahashi, S. I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H., *J. Org. Chem.*, **1987**, 52, 4319.
39. Chowdhury, R. L.; Backvall, J. E., *Chem. Commun.*, **1991**, 1063.
40. Almeida, M. L. S.; Beller, M.; Wang, G. Z.; Backvall, J. E., *Chem. Eur. J.*, **1996**, 2, 1533.
41. Morton, D.; Colehamilton, D. J., *Chem Commun.*, **1988**, 1154.
42. Wang, G. Z.; Backvall, J. E., *Chem. Commun.*, **1992**, 337.
43. Pamies, O.; Backvall, J. E., *Chem. Eur. J.*, **2001**, 7, 5052.
44. Laxmi, Y. R. S.; Backvall, J. E., *Chem. Commun.*, **2000**, 611.
45. Samec, J. S. M.; Backvall, J. E.; Andersson, P. G.; Brandt, P., *Chem. Soc. Rev.*, **2006**, 35, 237.
46. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R., *J. Am. Chem. Soc.* **1995**, 117, 7562.
47. Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R., *Angew. Chem. Int. Ed.*, **1997**, 36, 285.
48. Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R., *Angew. Chem. Int. Ed.*, **1997**, 36, 288.
49. Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R., *J. Am. Chem. Soc.*, **1996**, 118, 4916.
50. Wang, G. Z.; Backvall, J. E., *Chem. Commun.*, **1992**, 980.



51. Noyori, R.; Yamakawa, M.; Hashiguchi, S., *J. Org. Chem.*, **2001**, 66, 7931.
52. Noyori, R.; Ohkuma, T., *Angew. Chem. Int. Ed.*, **2001**, 40, 40.
53. Handgraaf, J. W.; Reek, J. N. H.; Meijer, E. J., *Organometallics.*, **2003**, 22, 3150.
54. Palmer, M. J.; Wills, M., *Tetrahedron-Asymmetry.*, **1999**, 10, 2045.
55. Fujita, K.; Yamaguchi, R., *Synlett.*, **2005**, 560.
56. Prince, R. H.; Rospin, K. A., *J. Chem. Soc., (A)*, **1969**, 612.
57. de Vries, J. G.; Roelfes, G.; Green, R., *Tetrahedron Lett.*, **1998**, 39, 8329.
58. Hanasaka, F.; Fujita, K.; Yamaguchi, R., *Organometallics.*, **2005**, 24, 3422.
59. Hanasaka, F.; Fujita, K. I.; Yamaguchi, R., *Organometallics.*, **2004**, 23, 1490.
60. Hillier, A. C.; Lee, H. M.; Stevens, E. D.; Nolan, S. P., *Organometallics.*, **2001**, 20, 4246.
61. Gnanamgari, D.; Moores, A.; Rajaseelan, E.; Crabtree, R. H., *Organometallics.*, **2007**, 26, 1226.
62. Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C., *J. Org. Chem.*, **2001**, 66, 9020.
63. Cho, C. S.; Kim, D. Y.; Shim, S. C., *Bull. Korean Chem. Soc.*, **2005**, 26, 802.
64. Morales-Morales, D.; Redon, R.; Wang, Z. H.; Lee, D. W.; Yung, C.; Magnuson, K.; Jensen, C. M., *Can. J. of Chem.*, **2001**, 79, 823.
65. Knorr, L., *Chem. Ber.*, **1884**, 17, 2863
66. Paal, C., *Chem. Ber.*, **1884**, 17, 2756
67. Paal, C., *Chem. Ber.*, **1885**, 18, 1545
68. Amarnath, V.; Amarnath, K., *J. Org. Chem.*, **1995**, 60, 301.
69. Stauffer, F.; Neier, R., *Org. Lett.*, **2000**, 2, 3535.
70. Kürti, L.; Czakó, B., *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: 2005.
71. Wolthuis, E.; Bossenbrock, B.; DeWall, G.; Geels, E.; Leedwater, A., *J. Org. Chem.* **1963**, 28, 567
72. Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C., *Tetrahedron.*, **1998**, 54, 1955.
73. Brown, R. C. D., *Angew. Chem. Int. Ed.*, **2005**, 44, 850.
74. Kirsch, S. F., *Org. Biomol. Chem.*, **2006**, 4, 2076.
75. Lu, X.; Ji, J., *Chem. Commun.*, **1993**, 764
76. Rao, H. S. P.; Jothilingam, S., *J. Org. Chem.*, **2003**, 68, 5392.
77. Marshall, J. A.; Robinson, E. D., *J. Org. Chem.*, **1990**, 55, 3450.

78. Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H., *J. Org. Chem.*, **1991**, *56*, 5816-5819.
79. Marshall, J. A.; Sehon, C. A., *J. Org. Chem.*, **1995**, *60*, 5966.
80. Seiller, B.; Bruneau, C.; Dixneuf, P. H., *Tetrahedron*, **1995**, *51*, 13089.
81. Gabriele, B.; Salerno, G.; Lauria, E., *J. Org. Chem.*, **1999**, *64*, 7687.
82. Hashmi, A. S. K., *Angew. Chem. Int. Ed.*, **1995**, *34*, 1581.
83. Kell'in, A. V.; Gevorgyan, V., *J. Org. Chem.*, **2002**, *67*, 95.
84. Kell'in, A. V.; Sromek, A. W.; Gevorgyan, V., *J. Amer. Chem. Soc.*, **2001**, *123*, 2074.
85. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G., *J. Org. Chem.*, **1991**, *56*, 6924.
86. Minetto, G.; Raveglia, L. F.; Taddei, M., *Org. Lett.*, **2004**, *6*, 389.
87. Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R., *J. Org. Chem.*, **2005**, *70*, 1471.
88. Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z., *Synlett*, **2003**, 75.
89. Chochois, H.; Sauthier, M.; Maerten, E.; Castanet, Y.; Mortreux, A., *Tetrahedron*, **2006**, *62*, 11740.
90. Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R., *Tetrahedron Lett.*, **2001**, *42*, 1339.
91. Gabriele, B.; Salerno, G.; Fazio, A., *J. Org. Chem.* **2003**, *68*, 7853.
92. Harrison, T. J.; Kozak, J. A.; Corbella-Pane, M.; Dake, G. R., *J. Org. Chem.*, **2006**, *71*, 4525.
93. Gorin, D. J.; Davis, N. R.; Toste, F. D., *J. Am. Chem. Soc.*, **2005**, *127*, 11260.
94. Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L., *Org. Lett.*, **2004**, *6*, 2957.
95. Braun, R. U.; Zeitler, K.; Muller, T. J. J., *Org. Lett.*, **2001**, *3*, 3297.
96. Dhawan, R.; Arndtsen, B. A., *J. Am. Chem. Soc.*, **2004**, *126*, 468.
97. Lu, Y. D.; Arndtsen, B. A., *Angew. Chem. Int. Ed.*, **2008**, *47*, 5430.
98. Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A., *J. Am. Chem. Soc.*, **2003**, *125*, 1474.
99. Meyer, K. H.; Schuster, K., *Chem. Ber.*, **1922**, *55*, 819.
100. Rupe, H.; Kambli, E., *Helv. Chim. Acta.*, **1926**, *9*, 672.

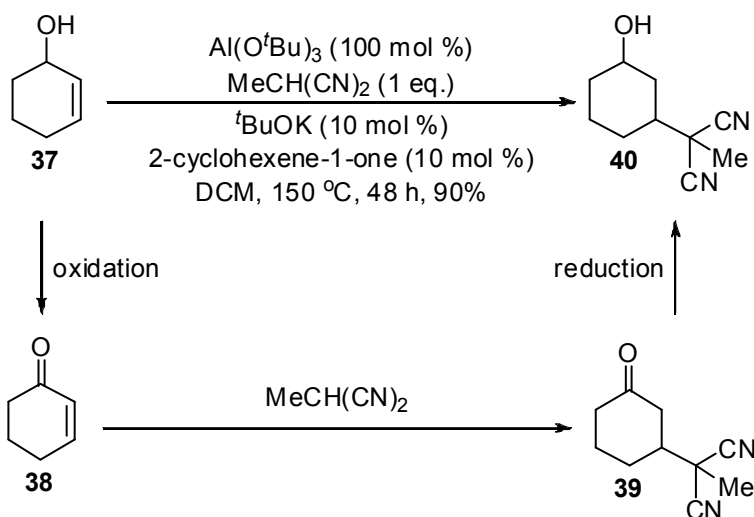
101. Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D., *J. Org. Chem.*, **1977**, *42*, 3403.
102. Hennion, G. F.; Davis, R. B.; Maloney, D. E., *J. Am. Chem. Soc.*, **1949**, *71*, 2813
103. Narasaka, K.; Kusama, H.; Hayashi, Y., *Chem. Lett.*, **1991**, 1413.
104. Lorber, C. Y.; Osborn, J. A., *Tetrahedron Lett.*, **1996**, *37*, 853.
105. Picquet, M.; Bruneau, C.; Dixneuf, P. H., *Chem Commun.*, **1997**, 1201.
106. Suzuki, T.; Tokunaga, M.; Wakatsuki, Y., *Tetrahedron Lett.*, **2002**, *43*, 7531.
107. Touchard, D.; Dixneuf, P. H., *Coord. Chem. Rev.*, **1998**, *180*, 409.
108. Puerta, M. C.; Valerga, P., *Coord. Chem., Rev.*, **1999**, *195*, 977.
109. Cadierno, V.; Diez, J.; Garcia-Garrido, S. E.; Gimeno, J., *Chem. Commun.*, **2004**, 2716.
110. Cadierno, V.; Garcia-Garrido, S. E.; Gimeno, J., *Adv. Synth. Catal.*, **2006**, *348*, 101.
111. Engel, D. A.; Dudley, G. B., *Org. Lett.*, **2006**, *8*, 4027.
112. Lee, S. I.; Back, J. Y.; Sim, S. H.; Chung, Y. K., *Synthesis.*, **2007**, 2107.
113. Ma, D.; Lu, X. Y., *Chem Commun.*, **1989**, 890.
114. Trost, B. M.; Livingston, R. C., *J. Am. Chem. Soc.*, **1995**, *117*, 9586.
115. Knoevenagel, E., *Chem. Ber.*, **1894**, *27*, 2596.
116. Knoevenagel, E., *Chem. Ber.*, **1986**, *29*, 1156.
117. Jones, G., *Org. React.* **1967**, *15*.
118. Apsimon, J. W.; Hooper, J. W.; Laishes, B. A., *Can. J. Chem.*, **1970**, *48*, 3064.
119. Shi, D. Q.; Wang, X. S.; Yao, C. S.; Mu, L. L., *J. Chem. Res. Synop.*, **2002**, 344.
120. Lehnert, W., *Tetrahedron Lett.*, **1970**, *54*, 4723.
121. Lehnert, W., *Tetrahedron.*, **1974**, *30*, 301-305.
122. Lehnert, W., *Synthesis.*, **1974**, 667.
123. Texierboullet, F.; Foucaud, A., *Tetrahedron Lett.*, **1982**, *23*, 4927.
124. Siebenhaar, B.; Casagrande, B.; Studer, M.; Blaser, H. U., *Can. J Chem.*, **2001**, *79*, 566.
125. Simpson, J.; Rathbone, D. L.; Billington, D. C., *Tetrahedron Lett.*, **1999**, *40*, 7031.
126. Balalaie, S.; Nemati, N., *Synth. Commun.*, **2000**, *30*, 869.
127. McNulty, J.; Steere, J. A.; Wolf, S., *Tetrahedron Lett.*, **1998**, *39*, 8013.
128. Ren, Z. J.; Cao, W. G.; Tong, W. Q., *Synth. Commun.*, **2002**, *32*, 3475.
129. Li, Y. Q.; Xu, X. M.; Zhou, M. Y., *Chin. Chem. Lett.*, **2003**, *14*, 448.

130. Su, C.; Chen, Z. C.; Zheng, Q. G., *Synth. Commun.*, **2003**, 33, 2817.
131. Doebner, O., *Chem. Ber.*, **1902**, 35, 1136.
132. Beutler, U.; Fuenfschilling, P. C.; Steinkemper, A., *Org. Process Res. Dev.* **2007**, 11, 341.
133. Tietze, L. F.; Zhou, Y. F., *Angew. Chem. Int. Ed.*, **1999**, 38, 2045.
134. Tietze, L. F., *Chem. Rev.*, **1996**, 96, 115.
135. Hann, A. C. O.; Lapworth, A., *J. Chem. Soc.*, **1904**, 85, 46.
136. Kinastowski, S.; Mroczyk, W., *Pol. J. Chem.*, **1984**, 58, 179.
137. Kinastowski, S.; Mroczyk, W., *Bull. Pol. Acad. Sci.-Chem.*, **1989**, 37, 109.

## 2 RESULTS AND DISCUSSION I

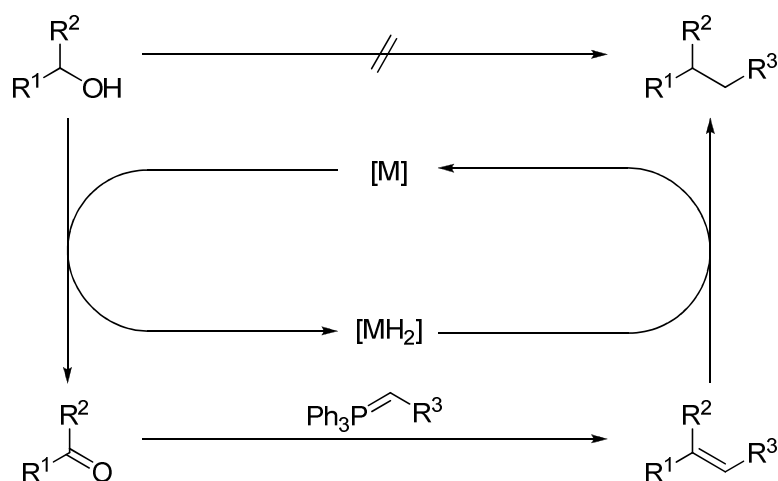
### 2.1 Background

Previous research in the Williams group has focused on the development of the “Catalytic Electronic Activation” methodology. Alcohols are inherently unreactive in nature with very few carbon-carbon or carbon heteroatom bond forming reactions resulting from alcohols. However the corresponding carbonyl compounds have a multitude of reactions where carbon-carbon or carbon heteroatom bonds are formed. Catalytic electronic activation temporarily enhances the electronic properties of a functional group allowing an otherwise unfeasible reaction to take place. These reactions have exploited the reversibility of transfer hydrogenation reactions as a way to augment the reactivity of alcohols by temporary oxidation to the corresponding carbonyl compound. This methodology has found the greatest use *via* nucleophilic attack of carbonyl compounds generated *in situ*. The first example of such a system was the addition of nucleophiles to allylic alcohols (**Scheme 54**).<sup>1</sup> In this process allylic alcohol **37** is oxidised by aluminium *tert*-butoxide to form the  $\alpha,\beta$ -unsaturated ketone **38** *in situ*, which is an excellent Michael acceptor allowing conjugate addition to take place with the desired nucleophile to form the intermediate ketone **39**. Subsequent restoration of the alcohol functionality *via* transfer hydrogenation completes the indirect addition to yield alcohol **40** in good yields.



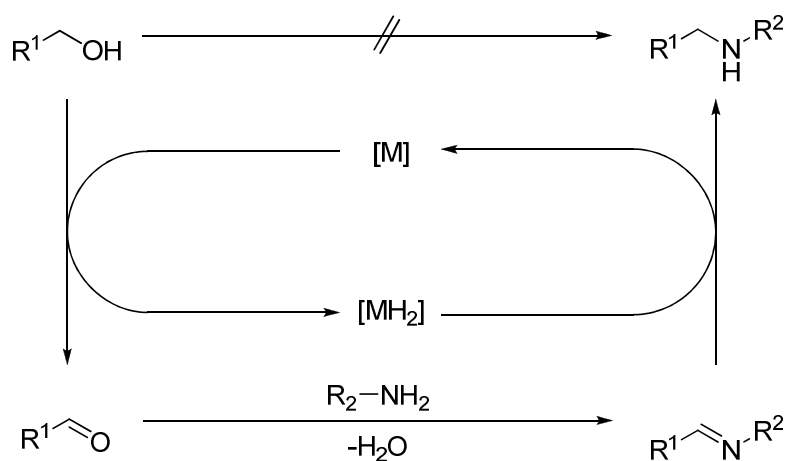
**Scheme 54.** Indirect nucleophilic addition to allylic alcohols.

The concept of “catalytic electronic activation” was further extended to the indirect formation of carbon-carbon bonds from alcohols utilising the Wittig and Horner-Wadsworth-Emmons olefinations.<sup>2-4</sup> The difference in these olefination reactions of alcohols is that there is no regeneration of the alcohol functionality at the end of the reaction cycle. Instead the hydrogen which is removed from the alcohol is used to reduce the alkene *via* transfer hydrogenation after the olefination step (**Scheme 55**). This process demonstrates the concept of “borrowing hydrogen”, a redox neutral process where the hydrogen removed in the initial oxidation step is returned in the reductive step. Key to the success of this chemistry is the ability of the catalyst to be compatible with the olefination reactions as well as possessing the ability to remove, store and return hydrogen.



**Scheme 55.** “Borrowing hydrogen” in an indirect olefination of alcohols.

“Borrowing hydrogen” methodology was also utilised in the preparation of amines *via* the aza-Wittig reaction.<sup>5</sup> Whilst the use of aza-ylides proved to be a useful method in the synthesis of secondary amines from alcohols, the reaction offered poor atom economy, with an equivalent of triphenylphosphine oxide side product formed. This problem was overcome by using amines directly as nucleophiles.<sup>6, 7</sup> In this process, imine formation by dehydration results in the only by-product of the reaction being water, proving to be a more atom efficient process (**Scheme 56**).



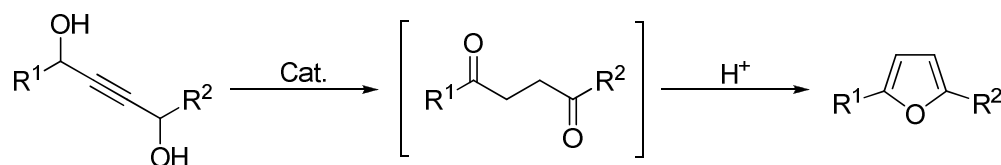
**Scheme 56.** Indirect *N*-alkylation of alcohols.

The idea of using transfer hydrogenation to activate a molecule to undergo a chemical reaction resulting in tandem and cascade reactions has been the underlying theme of research in the Williams group. A review has been published in the area by Williams *et al.*<sup>8</sup>

We were interested in using 1,4-alkyne diols as surrogates for 1,4-dicarbonyl in the Paal-Knorr furan synthesis. Limitations of the Paal-Knorr synthesis lie in the availability of the 1,4-dicarbonyl species (or their derivatives) and stability issues associated with these substrates (*vide supra*). There have been many reports detailing more elaborate approaches to the synthesis of furans using transition metal catalysts most involving cyclisation reactions of allenyl and alkynyl-ketones (*vide supra*) of which Yamamoto has reviewed comprehensively.<sup>9</sup> Of particular interest to us was the report by Lu *et al.* describing the palladium catalysed isomerisation of 1,4-alkyne diols to their respective 1,4-dicarbonyl compounds.<sup>10</sup> This was shortly followed by a further report describing that in the presence of an acid resin, *in situ* ring closure occurred to give the corresponding furan derivative.<sup>11</sup> This reaction required 4 mol% palladium at 130 °C to effect furan formation.

## 2.2 Aims

It appeared viable that using well known transfer hydrogenation catalysts known within the group, 1,4-alkyne diols could be converted to the requisite 1,4-dicarbonyl compounds either by intermolecular transfer hydrogenation or by concerted isomerisation. With addition of an acid co-catalyst it was deemed feasible that the 1,4-dicarbonyl compounds produced could be cyclised *in situ* to the furan derivatives in a one-pot, cascade route to 2,5-disubstituted furans (**Scheme 57**). This route seemed attractive as it would overcome the problems and difficulties associated with the Paal-Knorr route to furans.



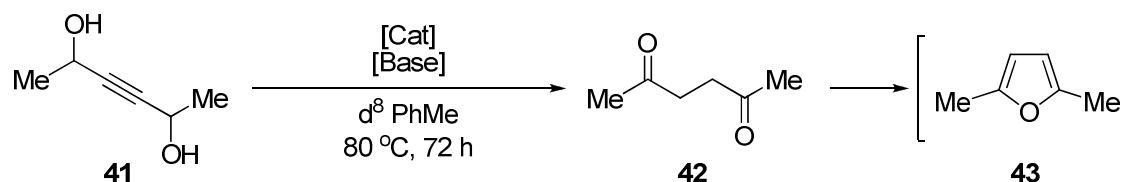
**Scheme 57.** Isomerisation/cyclisation approach to furans.

## 2.3 Initial Studies.

### Isomerisation of 1,4-Alkyne diols

Initial studies into the viability of using 1,4-alkyne-diols as 1,4-dicarbonyl surrogates focused on the iridium based catalysts [Ir(COD)Cl<sub>2</sub>]<sub>2</sub> **48** and [IrCp\*Cl<sub>2</sub>]<sub>2</sub> **50**. These catalysts are known within the group as transfer hydrogenation catalysts for olefin reductions<sup>4</sup> and seemed suitable candidates to carry out the isomerisation. Using commercially available 3-hexyne-2,5-diol **41**, NMR scale experiments were conducted. It was hoped that the conditions employed would result in formation of solely 2,5-hexadione **42** (**Scheme 58**). Use of 3-hexyne-2,5-diol **41** would allow for easy analysis due to the simplicity of the resulting NMR spectrum





**Scheme 58.** Initial NMR experiments.

100% conversion of starting material into products was achieved at 80 °C for 72 hours (**Table 1**). An interesting observation at this point was the formation of 2,5-dimethyl furan **43** under basic conditions. The formation of furan is known to proceed with the presence of a Lewis acid.<sup>12</sup> In this case the iridium catalysts could be acting as a Lewis acid to catalyse this step.

Entry <sup>a</sup>	Catalyst	Conversion % <sup>b</sup>	Ratio <b>42:43</b> % <sup>b</sup>
1	[Ir(COD)Cl <sub>2</sub> ] <sub>2</sub> <b>48</b>	100%	53:47
2	[IrCp*Cl <sub>2</sub> ] <sub>2</sub> <b>50</b>	100%	32:67

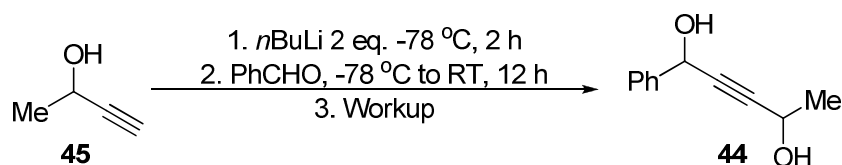
<sup>a</sup> Reactions carried out of NMR scale 0.1 mmol. 5 mol % catalyst loading. 10 mol % Cs<sub>2</sub>CO<sub>3</sub>. 10 mol% DPPP ligand was used with the [Ir(COD)Cl<sub>2</sub>]<sub>2</sub> catalyst. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy

**Table 1.** Initial iridium catalysed isomerisation experiments.

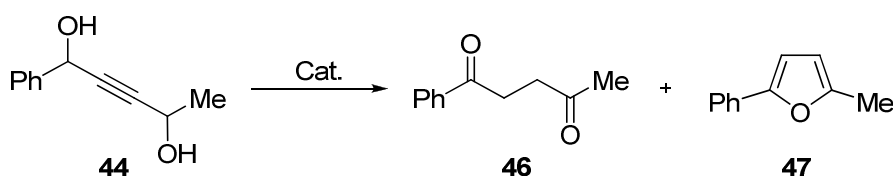
Even though these initial results were very promising there were a couple of downfalls associated with using these catalyst systems. Firstly, they require base to form the active transfer hydrogenation species, an obvious problem when we wanted to combine an acid catalysed cyclisation step after the initial isomerisation (although furan formation was possible without an acid co-catalyst). Secondly, these systems require long reaction times to achieve 100% conversion.

A wider range of catalysts was investigated after the initial hit using iridium systems. It was decided at this time not to abandon the base activated iridium systems as they showed a significant ability to facilitate furan formation. These iridium systems were compared with known ruthenium and rhodium transfer hydrogenation catalysts.<sup>13</sup>

(**Table 2**) 1-Phenyl-pent-2-yne-1,4-diol **44** was used in this screen due to the lower volatility of the diketone and furan products allowing for easier work up. 1-phenyl-pent-2-yne-1,4-diol **44** was synthesised from commercially available 3-butyn-2-ol **45** and benzaldehyde (**Scheme 59**). The results of the screen (**Scheme 60**) are shown in **Table 2**.



**Scheme 59.** 1-Phenyl-pent-2-yne-1,4-diol synthesis



**Scheme 60.** Initial catalyst screen.

Catalyst <sup>a</sup>	Temp(°C)/Time(h)	Conversion(%) <sup>b</sup>	46:47 <sup>b</sup>
[Ir(COD)Cl <sub>2</sub> ] <sub>2</sub> <b>48</b> /dppp <b>49</b> <sup>c</sup>	110/42	83	57:31
[IrCp*Cl <sub>2</sub> ] <sub>2</sub> <b>50</b> <sup>d</sup>	110/42	95	87:8
[RhCp*Cl <sub>2</sub> ] <sub>2</sub> <b>51</b> <sup>d</sup>	110/42	22	22:0
Rh(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <b>52</b> /dppp <b>49</b>	110/42	37	14:22
Grubbs' 1 <sup>st</sup> Generation <b>53</b> <sup>e</sup>	80/24	38	28:10
[Ru(Cymene)Cl <sub>2</sub> ] <sub>2</sub> <b>54</b> /dppf <b>33</b> <sup>d</sup>	80/24	56	36:20
Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> <b>55</b> /dppp <b>49</b>	80/24	21	21:0

<sup>a</sup> Reaction conditions: alkyne diol (1 mmol) was dissolved in PhMe (1 mL) in the presence of the catalyst (5mol % Ir, Rh or Ru) and ligand (5 mol %) and heated. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. <sup>c</sup> Cs<sub>2</sub>CO<sub>3</sub> (5 mol %) added. <sup>d</sup> Cs<sub>2</sub>CO<sub>3</sub> (10 mol %) added. <sup>e</sup> Grubbs' 1<sup>st</sup> generation metathesis catalyst; (Ru(PCy<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub>(=CHPh) addition of base makes the active transfer hydrogenation species).

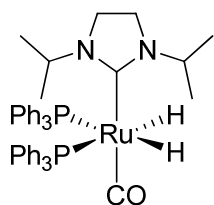
**Table 2.** Preliminary catalyst screen using a range of known transfer hydrogenation catalysts.

The iridium systems gave favourable conversions of starting 1,4-alkyne diol **44** into 1,4-diketone **46**. In comparison the ruthenium systems used showed poor conversion but

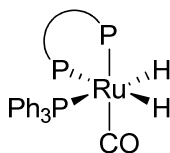
considering these reactions are conducted at only 80 °C for 24 hours instead of 42 hours at 110 °C ruthenium based systems showed the greater activity.

## 2.4 Ruthenium Catalysed Isomerisation of 1,4-Alkyne diols.

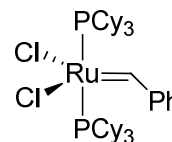
All the catalysts screened showed activity for the isomerisation reaction, and in most cases proceeded further to afford furan **47** as well as the diketone **46**. The ruthenium complexes showed somewhat greater catalytic activity, facilitating the reaction at 80 °C. The iridium systems screened show no catalytic activity at 80 °C. Ruthenium catalysts have also been shown to perform a variety of rearrangement reactions on propargylic alcohols.<sup>14</sup> A wide range of ruthenium systems was screened using 1-phenyl-pent-2-yne-1,4-diol **44** as the model substrate at 80 °C for 24 hours (**Table 3**).



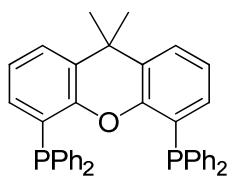
Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)(H<sub>2</sub>)(Ipr) **56**



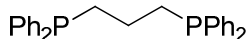
Ru(PPh<sub>3</sub>)(xantphos)(CO)(H<sub>2</sub>) **57**



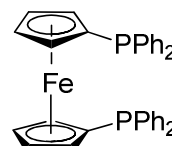
Grubbs' 1<sup>st</sup> Generation **53**



xantphos **58**



dppp **49**



dppf **33**

Entry <sup>a</sup>	Catalyst	46 (%) <sup>b</sup>	47 (%) <sup>b</sup>	Conversion (%) <sup>b</sup>
1	Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> (Ipr) <b>56</b>	23	4	27
2	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> <b>59</b> /xantphos <b>58</b> <sup>d</sup>	25	16	41
3	[Ru(xantphos)(PPh <sub>3</sub> )(CO)H <sub>2</sub> ] <b>57</b>	60	25	85
4	Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> <b>55</b> /dppp <b>49</b>	0	0	0
5	Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> <b>55</b> /dppf <b>33</b>	21	0	21
6	Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> <b>55</b> /PCy <b>59</b>	15	1	16
7	Ru(PPh <sub>3</sub> ) <sub>3</sub> Cl <sub>2</sub> <b>15</b> <sup>c</sup>	39	27	66
8	Grubbs' 1 <sup>st</sup> Generation <b>53</b> <sup>c</sup>	48	11	59
9	Ru(PPh <sub>3</sub> ) <sub>3</sub> Cl <sub>2</sub> <b>15</b> /xantphos <b>58</b> <sup>c</sup>	22	3	25
10	[Ru(COD)Cl <sub>2</sub> ] <sub>2</sub> /xantphos <b>58</b> <sup>d</sup>	5	18	13

<sup>a</sup> Reactions carried out on 0.5 mmol scale, 5 mol % ruthenium 80 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> 10 mol % LiOH.H<sub>2</sub>O added. <sup>d</sup> 5 mol % K<sub>2</sub>CO<sub>3</sub> added.

**Table 3.** Ruthenium catalyst screen.

The preformed ruthenium xantphos complex (**Table 3, entry 3**) gave the best result with 85% conversion with 60% diketone present. At this stage the criteria to perform the one-pot cascade reaction forced us to disregard catalysts that require bases to convert the catalyst precursor into the active catalytic species, as they would be incompatible with the acid catalysed cyclisation step. The group had previously observed remarkable catalyst acceleration when bidentate ligands have been employed in conjunction with ruthenium catalysts.<sup>15</sup> This is demonstrated in the isomerisation reaction by the ruthenium xantphos complex shown in **Table 3, entry 3**. We therefore concentrated our efforts on optimising the conditions using the ruthenium dihydride complex Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55**, with a range of ligands to improve catalytic activity. This particular catalyst also had the advantage of not requiring base to form the active catalytic species, already being in the dihydride form.

## 2.5 Optimisation

A range of ligands with the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  catalyst **58** was screened in an attempt to improve catalytic activity (**Table 4**). The catalyst systems screened previously (**Table 3**, **entries 4-6** and **9**) were screened in parallel again for consistency and for ease of direct comparison of catalytic activity at the given conditions. (**Table 4**)

Entry <sup>a</sup>	Ligand	46 (%) <sup>b</sup>	47 (%) <sup>b</sup>	Conversion (%) <sup>b</sup>
1	None	21	0	21
2	PCy <sub>3</sub> <b>59</b>	16	1	17
3	Dppp <b>49</b>	0	0	0
4	Dppf <b>33</b>	22	4	26
5	Xantphos <b>58</b>	56	12	68
6	Xantphos <b>58</b> <sup>c</sup>	18	63	81

<sup>a</sup> Reaction conditions: 1-phenyl-pent-2-yne-1,4-diol **44** (1 mmol) was dissolved in PhMe (1 mL) in the presence of  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** catalyst (5 mol %) and ligand (5 mol %) and heated at 80 °C for 24 h. <sup>b</sup> Analysis by <sup>1</sup>H NMR. <sup>c</sup> Reaction with 5 mol % AcOH.

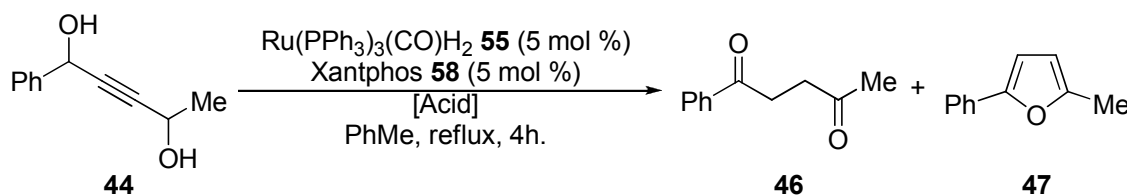
**Table 4.** Ligand screen with  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** as catalyst.

The reactions with no ligand present (**Table 4**, **entry 1**) and with addition of tricyclohexylphosphine **59** (**Table 4**, **entry 2**) and dppp {1,3-bis(diphenylphosphino)propane} **49** (**Table 4**, **entry 3**) resulted in no or poor conversion, with the dppp ligand completely shutting down the isomerisation reaction. Addition of ligands possessing wider bite angles such as dppf {1,1'-bis(diphenylphosphino)ferrocene} **33** (**Table 4**, **entry 4**) showed improvement. However, it was the xantphos ligand **58** developed by van Leeuwen *et al.*,<sup>16</sup> that showed the best catalytic activity, providing acceptable conversion of 1-phenyl-pent-2-yne-1,4-diol **44** to diketone **46** with additional furan **47** formation. On repeating the reaction with inclusion of 5 mol % of acetic acid co-catalyst, conversion of the substrate 1-phenyl-pent-2-yne-1,4-diol **44** proceed to 81% with 63% being the furan **47** (**Table 4**, **entry 6**). This finding was supportive of the acidic conditions needed to afford furan by cyclisation of the diketone intermediate. Therefore ruthenium dihydride complex  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** with xantphos **58** and acid co-catalyst provides a favourable

catalytic system for the isomerisation of alkyne diols into diketones with subsequent cyclisation to furans.

## 2.6 Acid Screen

Using the combination of  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** with xantphos **58** (**Scheme 61**) a range of different acids (organic, mineral and Lewis acids) was screened in order to establish a suitable acid co-catalyst. A huge range of acid and Lewis acid catalysts have been used to facilitate furan formation.<sup>12</sup> The acids chosen were deemed to be appropriately compatible with the ruthenium xantphos isomerisation system. At this point it was decided that conducting the reactions in toluene at reflux would increase the reaction rate allowing us to achieve even greater conversions, as well as allowing the cyclocondensation step to take place. After four hours the reaction was stopped and analysed by  $^1\text{H}$  NMR spectroscopy (**Table 5**).



Scheme 61. Acid screening

Entry <sup>a</sup>	Acid/Base <sup>b</sup>	46 (%) <sup>c</sup>	47 (%) <sup>c</sup>	Conversion (%) <sup>c</sup>
1	Acetic Acid	23	68	91
2	Propionic Acid	21	71	92
3	Benzoic Acid	21	71	92
4	Toluic Acid	20	68	88
5	Formic Acid	11	12	23
6	<i>p</i> -TsOH	0	0	0
7	H <sub>2</sub> SO <sub>4</sub>	0	0	0
8	TFA	0	0	0
9	Sc(OTf) <sub>3</sub>	3	3	6
10	<sup>t</sup> BuOK	57	2	59

<sup>a</sup> Reaction conditions: 1-phenyl-pent-2-yne-1,4-diol **44** (1 mmol) was dissolved in PhMe (1 mL) in the presence of Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> catalyst (5 mol %) and xantphos (5 mol %) and heated at 115 °C for 4 h. <sup>b</sup> 5 mol % loadings in all cases. <sup>c</sup> Analysed by <sup>1</sup>H NMR spectroscopy.

Table 5. Results of acid co-catalyst screen.

We found that a range of carboxylic acids could be used (Table 5, entries 1-5), including acetic, propionic, benzoic and toluic acids. However stronger acids such as toluenesulfonic acid, trifluoroacetic acid and sulphuric acid completely hindered the isomerisation step. Addition of scandium triflate, a common Lewis acid catalyst, also displayed poor conversion. Interestingly, use of a base such as potassium *tert*-butoxide as an additive afforded the diketone **46** as the major product (Table 5, entry 10).

The best parameters for the reaction at this time proved to be 5 mol% catalyst and ligand loading in toluene at reflux for 4 hours with 5 mol% of a carboxylic acid co-catalyst. With the increase in temperature it was deemed suitable to lower the catalyst and ligand loading to 1 mol %. To compensate for the lower catalyst loading the

reaction time was increased to 24 hours. This was an attractive trade off due to the requirement of 5 times less catalyst and ligand. Using these conditions a final screen of acid concentration using acetic acid as the model acid co-catalyst was used. (**Table 6**)

Entry <sup>a</sup>	AcOH (mol %)	46 (%) <sup>b</sup>	47 (%) <sup>b</sup>	Conversion (%) <sup>b</sup>
1	5	31	67	99
2	10	26	72	98
3	15	20	75	95
4	20	17	73	90

<sup>a</sup> Reaction conditions: 1-phenyl-pent-2-yne-1,4-diol **44** (1 mmol) was dissolved in PhMe (1 mL) in the presence of Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> catalyst (1 mol%) and xantphos (1 mol %) and heated at 115 °C for 24 h. <sup>b</sup> Analysed by <sup>1</sup>H NMR spectroscopy.

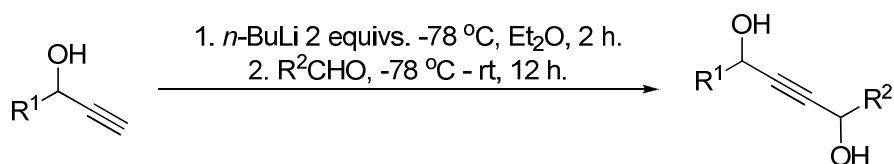
**Table 6.** Screen with changing acid co-catalyst concentration.

From **Table 6** we can see that increasing the concentration of acid co-catalyst beyond 10 mol % begins to degrade the conversion but marginally favours formation of furan. In balancing all the factors of the reaction a standard set of conditions was decided on as; Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55** 1 mol %, xantphos **58** and 5 mol % of acid co-catalyst (RCO<sub>2</sub>H).

## 2.7 Synthesis of 1,4-Alkyne diols

To ensure that 1,4-alkyne diols are suitable surrogates for 1,4-dicarbonyl compounds that they must be easily accessible, with a simple synthesis with a wide functional group tolerance and diversity. 1,4-Alkyne diols were prepared by treatment of commercially available propargylic alcohols with 2 equivalents of *n*-butyllithium, followed by addition of the appropriate aldehyde. These reactions were not optimised. As a result a wide range of alkyne diols was synthesised in modest to good yields (**Scheme 62**, **Table 7**).





Scheme 62. Synthesis of 1,4-Alkyne Diols.

Entry <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	1,4-Alkyne diol	Yield (%) <sup>b</sup>
1	Me	Ph	<b>44</b>	82
2	Me	<sup>n</sup> Pr	<b>60</b>	65
3	Me	<sup>i</sup> Pr	<b>61</b>	63
4	Me	<sup>t</sup> Bu	<b>62</b>	78
5	Me	CH <sub>2</sub> CH <sub>2</sub> Ph	<b>63</b>	51
6	H	Ph	<b>64</b>	52
7	Ph	<sup>t</sup> Bu	<b>65</b>	74
8	Ph	CH <sub>2</sub> CH <sub>2</sub> Ph	<b>66</b>	35
9	Me	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>67</b>	57
10	Me	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>68</b>	46
11	Me	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>69</b>	59
12	Me	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>70</b>	58
13	Me	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>71</b>	58
14	Me	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>72</b>	48
15	Me	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	<b>73</b>	55
16	Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>74</b>	64
17	Me	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>75</b>	44
18	Me	Naphthyl-	<b>76</b>	70
19	Me	2-Furyl-	<b>77</b>	38
20	Me	2-Thienyl-	<b>78</b>	22

<sup>a</sup> Reactions carried out of 30 to 60 mmol scale. <sup>b</sup> Isolated yields after purification by column chromatography.

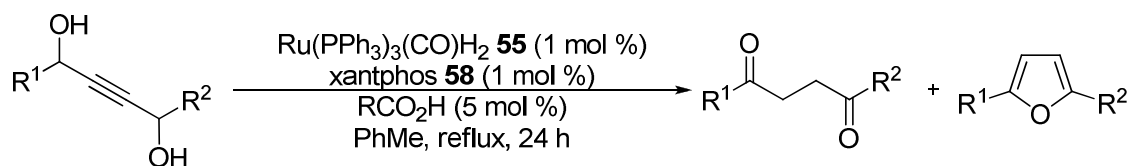
Table 7. 1,4-Alkynediols synthesised.

A range of 1,4-Alkyne diols was successfully synthesised using the simple protocol of using *n*-butyl lithium and commercially available propargylic alcohols with suitable

aldehydes. Alkyl-alkyl substituted 1,4-alkynediols (**Table 7, entries 2-5**) were successfully synthesised as well as aryl/alkyl (**Table 7 entries 6-7**) substituted alkyne diols. Similarly, a variety of differently substituted aryl/alkyl alkyne diols were also synthesised, including a range of halogenated compounds include *ortho*, *meta* and *para* substituted halogenated alkyne diols (**Table 7 entries 9, 10 and 14**). Electron withdrawing and electron donating groups were also incorporated into the aryl/alkyl 1,4-alkynediols (**Table 7, entries 15-18**). Finally a naphthyl substituted alkyne diol **77** was also successful as well as the heteroaromatic 2-furyl **78** and 2-thienyl **79** compounds. This range of 1,4-alkyne diols, when subjected to the furan forming conditions would allow access to a variety of variously substituted 2,5-furan derivatives.

## 2.8 Synthesis of 2,5-Disubstituted Furans.

With a suitable and efficient system in place for the isomerisation and cyclisation of 1,4-alkyne diols into the furan derivatives the 1,4-alkyne diols synthesised were converted into 2,5-disubstituted furans (**Scheme 63**).



**Scheme 63.** Optimised conditions for furan synthesis from 1,4-alkyne diols

The range of alkyl/alkyl and aryl/alkyl substituted 1,4-alkyne diols were converted into the required furan derivatives with good to excellent selectivity and with good functional group tolerance (**Table 8**).

Entry <sup>a</sup>	1,4-Alkyne diol	R <sup>1</sup>	R <sup>2</sup>	Conversion (%) <sup>b</sup>	Diketone (%) <sup>b</sup>	Furan (%) <sup>b</sup>	Compound N <sup>o</sup>
1	<b>44</b>	Me	Ph	100	15	85 (80) <sup>e</sup>	<b>79</b>
2	<b>60</b>	Me	<sup>n</sup> Pr	95 <sup>d</sup>	22 <sup>d</sup>	73 <sup>d</sup>	<b>80</b>
3	<b>61</b>	Me	<sup>i</sup> Pr	94 <sup>d</sup>	15 <sup>d</sup>	79 <sup>d</sup>	<b>81</b>
4	<b>62</b>	Me	<sup>t</sup> Bu	100 <sup>d</sup>	7 <sup>d</sup>	93 <sup>d</sup>	<b>82</b>
5	<b>63</b>	Me	CH <sub>2</sub> CH <sub>2</sub> Ph	100 <sup>d</sup>	9 <sup>d</sup>	91 <sup>d</sup>	<b>83</b>
6	<b>64</b>	H	Ph	100	4	96	<b>84</b>
7	<b>65</b>	Ph	<sup>t</sup> Bu	100 <sup>c</sup>	20	80	<b>85</b>
8	<b>66</b>	Ph	CH <sub>2</sub> CH <sub>2</sub> Ph	100 <sup>c</sup>	24	76	<b>86</b>
9	<b>67</b>	Me	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	100	23	77 (58) <sup>e</sup>	<b>87</b>
10	<b>68</b>	Me	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	100	18	82 (77) <sup>e</sup>	<b>88</b>
11	<b>69</b>	Me	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	100 <sup>c</sup>	19	81 (59) <sup>e</sup>	<b>89</b>
12	<b>70</b>	Me	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	100 <sup>c</sup>	19	81 (59) <sup>e</sup>	<b>90</b>
13	<b>71</b>	Me	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	100	23	77 (67) <sup>e</sup>	<b>91</b>
14	<b>72</b>	Me	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	100	17	83	<b>92</b>
15	<b>73</b>	Me	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	100	12	88 (63) <sup>e</sup>	<b>93</b>
16	<b>74</b>	Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	100	20	80 (64) <sup>e</sup>	<b>94</b>
17	<b>75</b>	Me	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	50 <sup>c</sup>	10	40	<b>95</b>
18	<b>76</b>	Me	Naphthyl-	100	18	82 (70) <sup>e</sup>	<b>96</b>
19	<b>77</b>	Me	2-Furyl-	100	19	81	<b>97</b>
20	<b>78</b>	Me	2-Thienyl-	100	22	78	<b>98</b>

<sup>a</sup> Reactions conducted on 1 mmol scale. <sup>b</sup> determined by <sup>1</sup>H NMR analysis, and using benzoic acid co-catalyst (5 mol %). <sup>c</sup> Using propionic acid co-catalyst (5 mol %). <sup>d</sup> Analysed by GC. <sup>e</sup> Yields in parentheses are isolated yields after column chromatography.

**Table 8.** Conversion of 1,4-Alkyne diols into 2,5 disubstituted furans.

The majority of the substrates reacted showed conversions greater than 95% with greater than 70% furan produced. In the majority of cases the amount of 2,5-furan produced was greater than 80%. It was only the 1,4-alkyne diol containing the *para* substituted nitro group that proved problematic. The reaction seemed to halt at 50% conversion. Issues with compatibility of the nitro group with ruthenium catalysts have been encountered by the Williams group before. Additionally the 1,4-alkyne diol

containing the *para*-substituted nitro group was only sparingly soluble in toluene at reflux, which would undoubtedly hinder the conversion of starting material into product, not being a true homogeneous reaction.

## 2.9 Chapter summary

- Established an isomerisation reaction of 1,4-alkyne diols using  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** (1 mol%) coupled with the xantphos ligand **58** (1 mol%) to afford the 1,4 diketones.
- With addition of 5 mol% of organic acid co-catalyst such as acetic, propionic and benzoic acid 2,5-disubstituted furans were synthesised from 1,4-alkyne diols, *via* the cyclocondensation of the 1,4-diketone *in situ*.
- A range of 1,4-Alkyne diols were synthesised with various functional groups present to establish the utility of 1,4-alkyne diols as 1,4-dicarbonyl surrogates.
- Using the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** and xantphos **58** catalytic system coupled with an organic co-catalyst a range of 2,5-disubstituted furan derivatives were synthesised in modest to good yields in one tandem reaction.
- The results of this study have been published.<sup>17</sup>

**2.10 References**

1. Black, P. J.; Edwards, M. G.; Williams, J. M. J., *Tetrahedron.*, **2005**, *61*, 1363.
2. Edwards, M. G.; Williams, J. M. J., *Angew. Chem.-Int. Ed.*, **2002**, *41*, 4740.
3. Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D., *Chem. Commun.*, **2004**, 90.
4. Black, P. J.; Edwards, M. G.; Williams, J. M. J., *Eur. J. Org. Chem.*, **2006**, 4367.
5. Cami-Kobeci, G.; Williams, J. M. J., *Chem. Commun.*, **2004**, 1072.
6. Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J., *Bioorg. Med. Chem.*, **2005**, *15*, 535.
7. Hamid, M.; Williams, J. M. J., *Chem. Commun.*, **2007**, 725.
8. Hamid, M.; Slatford, P. A.; Williams, J. M. J., *Adv. Synth. Catal.*, **2007**, *349*, 1555.
9. Patil, N. T.; Yamamoto, Y., *Arkivoc* **2007**, 121.
10. Lu, X. Y.; Ji, J. G.; Ma, D. W.; Shen, W., *J. Org. Chem.*, **1991**, *56*, 5774.
11. Ji, J. G.; Lu, X. Y., *Chem Commun.*, **1993**, 764.
12. Kürti, L.; Czakó, B., *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: 2005.
13. Gladiali, S.; Alberico, E., *Chem. Soc. Rev.*, **2006**, *35*, 226.
14. Cadierno, V.; Crochet, P.; Gimeno, J., *Synlett.*, **2008**, 1105.
15. Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J., *Tetrahedron Lett.*, **2006**, *47*, 6787.
16. Kamer, P. C. J., van Leeuwen, P. W. N., Reek, J. N. H., *Acc. Chem. Res.*, **2001**, *34*, 895.
17. Pridmore, S. J.; Slatford, P. A.; Williams, J. M. J., *Tetrahedron Lett.*, **2007**, *48*, 5111.

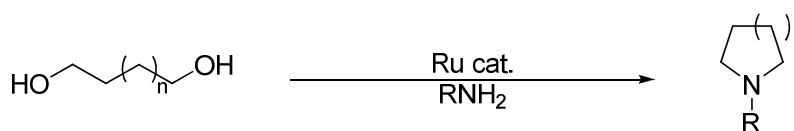
### 3 RESULTS AND DISCUSSION II

#### 3.1 Aim

To use the established ruthenium xantphos catalysed isomerisation of 1,4-alkyne diols in the synthesis of 1,2,5-trisubstituted pyrroles.

#### 3.2 Background

The conversion of simple diols into saturated *N*-substituted heterocycles using ruthenium based catalysts has been reported by several groups<sup>1,2</sup> including the Williams group.<sup>3</sup> The key to this chemistry is the ruthenium catalysed oxidation of a diol to give an aldehyde. Reaction *in situ* with an amine results in formation of an imine, which is reduced to the amine. This cycle is repeated resulting in cyclisation (**Scheme 64**).



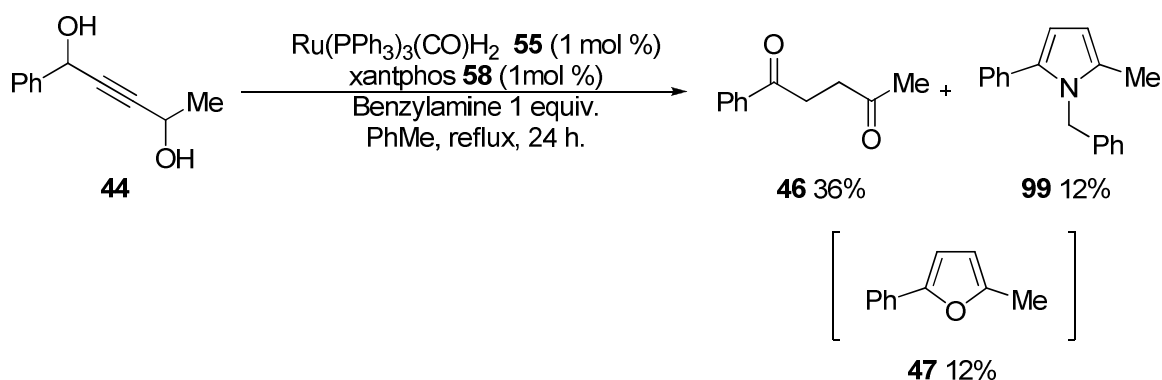
**Scheme 64.** General route to saturated *N*-substituted heterocycles.

Using  $Ru(PPh_3)_3(CO)H_2$  **55** with the bidentate phosphine ligand xantphos **58** we were able to effect isomerisation of 1,4-alkyne diols to 1,4-dicarbonyl compounds, with *in situ* cyclisation to the furan derivatives. (*vide supra*). By replacing the organic acid co-catalyst used in the furan system with stoichiometric amine, a route to pyrroles could be achieved using 1,4-alkyne diols as the 1,4-dicarbonyl surrogates with *in situ* *N*-heterocyclisation as an alternative to the traditional Paal-Knorr reaction. There exists one previous report of the transition metal catalysed conversion of 1,4-alkyne diols into a pyrrole using  $Ru(PPh_3)_3Cl_2$  **15** as a catalyst. However this system requires 150 °C to effect isomerisation and 63% conversion was the best case in this example. This system also would not work when anilines were used as the amine components.<sup>4</sup>

Since the combination of  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** with xantphos **58** had proven to be successful for the isomerisation of 1,4-alkyne diols into 1,4-diketones and furans, it was deemed to be a sensible system to conduct the isomerisation 1,4-alkyne diols into 1,4-diketones with subsequent cyclisation to pyrroles employing a suitable amine.

### 3.3 Initial Studies

Gratifyingly, as the isomerisation of 1,4-alkyne diols was established and optimised there was little need to investigate any change in parameters for this step, rather focus was directed at the cyclocondensation between the resulting 1,4-diketones with a suitable amine. Using  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** with xantphos **58** at 1 mol% concentration with 1-phenyl-pent-2-yne-1,4-diol **44** as the model substrate, 1 equivalent of benzylamine was added to the reaction with the hope of facilitating both the isomerisation reaction and the subsequent cyclisation to afford *N*-benzyl-2-phenyl-5-methyl pyrrole **99** (Scheme 65).



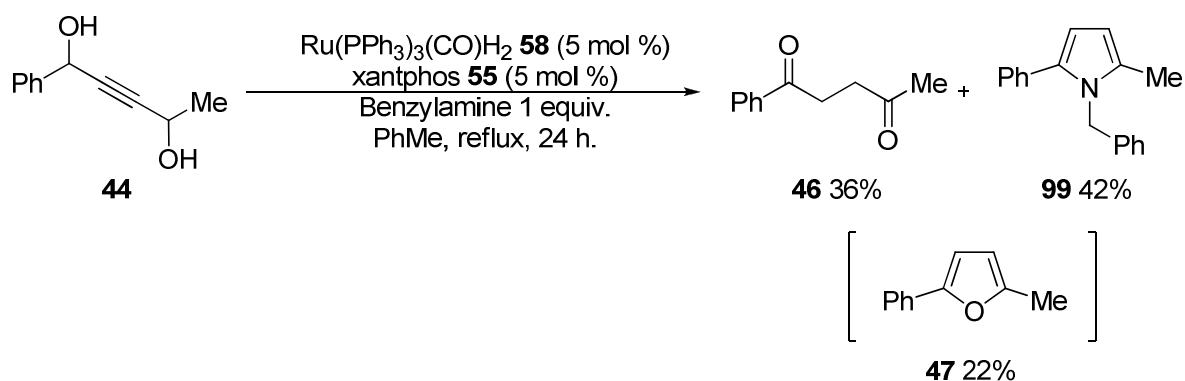
**Scheme 65.** Initial reaction investigating pyrrole formation.

By  $^1\text{H}$  NMR analysis of the reaction in **Scheme 65** we found that only 60% conversion was achieved and the distribution of desired products was poor. There was a significant amount of 1,4 diketone **46** remaining indicating that one equivalent of benzylamine was insufficient in facilitating the cyclocondensation step. Similarly, there was as much furan side product **47** formed as there was pyrrole **99** formation. This again suggested



that one equivalent of benzylamine nucleophile was not enough to allow the second step of the tandem reaction to occur. Similarly the Lewis acidic nature of the ruthenium based catalysts could be facilitating the furan formation. Another issue was the low conversion of the isomerisation step. Under the conditions used for furan formation using 1 mol% catalyst loading the conversion of starting 1,4-alkyne diol into 1,4-diketone and furan was typically greater than 95%. With addition of benzylamine to the reaction, the isomerisation step is considerably hindered resulting in poor conversion. If the isomerisation step were being hindered any subsequent pyrrole formation would also suffer from low conversion.

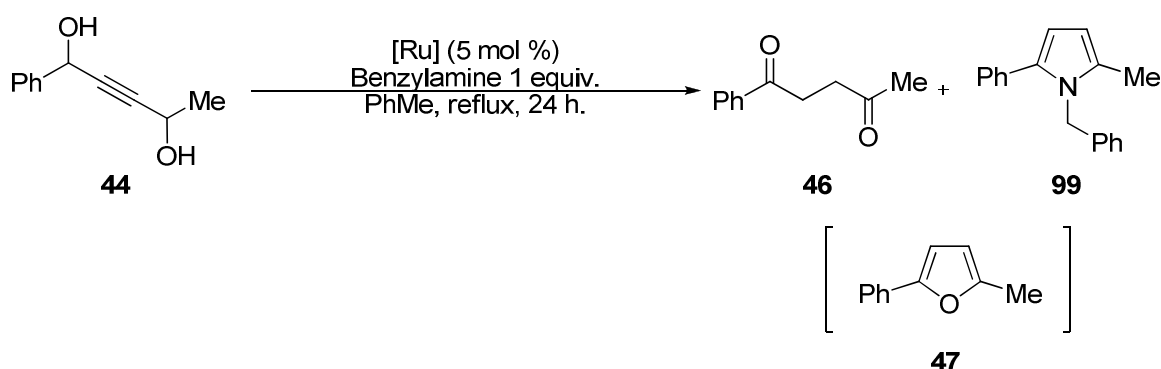
A repeat of the reaction shown in (Scheme 65) using 5 mol% catalyst loading was conducted in order to push the isomerisation step to completion and then allow us to evaluate the cyclocondensation step with a suitable amine (Scheme 66).



**Scheme 66.** Pyrrole forming reaction using higher catalyst loading.

Using a catalyst and ligand loading of 5 mol % immediately gave us 100% conversion establishing the fact that the isomerisation step is possible with amine present, but also showing that the amine component could be hindering the isomerisation step. The product distribution was improved favouring pyrrole formation, but with significant unreacted 1,4-diketone **46** present as well as a significant amount of furan **47** formation, probably as a consequence of the increased  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  **55** loading.

At this point it was pertinent to consult the literature in an effort to overcome these initial problems. Watanabe used  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** to afford isomerisation and cyclisation of 1,4-alkyne diols to limited effect.<sup>4</sup> A direct comparison of Watanabe's  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** system and the current  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** system was conducted (**Scheme 67**). Watanabe's system required a catalyst loading of only 1 mol% but a temperature of 150 °C for 5 hours. It is known that addition of base to the  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** greatly enhances its catalytic activity through replacement of metal-halide bond with the more reactive metal hydride bond.<sup>5,6</sup> Therefore using  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** at 5 mol% loading and with addition of caesium carbonate a comparison against the ruthenium xantphos system was conducted (**Scheme 67**, **Table 9**).



**Scheme 67.** Comparison of Watanabe's system with the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ /xantphos catalyst

Entry <sup>a</sup>	Catalyst System <sup>b</sup>	Conversion (%) <sup>c</sup>	<b>46</b> (%) <sup>c</sup>	<b>47</b> (%) <sup>c</sup>	<b>99</b> (%) <sup>c</sup>
1	$\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ <b>55</b> /xantphos <b>58</b>	100	8	14	78
2	$\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ <b>15</b> / $\text{Cs}_2\text{CO}_3$	100	9	13	82

<sup>a</sup> Reactions carried out on 1 mmol scale. <sup>b</sup> Catalyst loading at 5 mol %. The  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  catalyst required 10 mol %  $\text{Cs}_2\text{CO}_3$  loading, no additional ligand was included. <sup>c</sup> Analysed by  $^1\text{H}$  NMR spectroscopy.

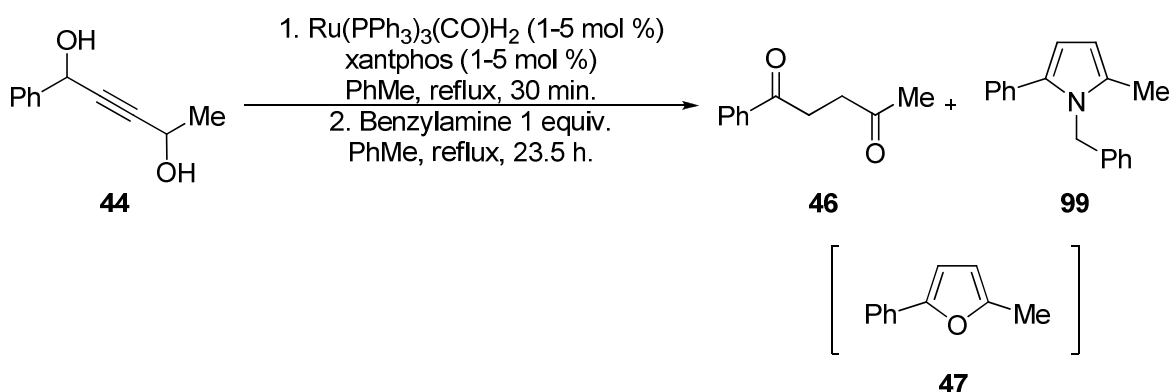
**Table 9.** Results of the ruthenium catalyst comparison.

There is very little to choose between the catalyst systems used. Both achieved 100% at the elevated catalyst loadings in toluene at reflux, and both systems gave good conversion of 1,4-alkyne diol **44** to 1,4-diketone **46** and then to the pyrrole product **99**. In comparison to the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ /xantphos system which is performed in the

absence of base, the addition of  $\text{Cs}_2\text{CO}_3$ , neither hindered nor enhanced reactivity and conversions with both systems producing equivalent amounts of furan **47** side product. We hoped that in such cases addition of a base such as caesium carbonate present may deter furan formation, but it had essentially no influence on product distribution. Optimisation of this transformation would be conducted with the already successful  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ /xantphos isomerisation catalyst and focus would be on the cyclocondensation process in order to favour pyrrole formation.

### 3.4 Optimisation

Using 5 mol % loading of  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** and xantphos **58** is excessive when compared to only needing 1 mol % loading in the case of the furan chemistry. A screen of catalyst loadings was conducted for the tandem reaction. Previously in the group the approach of pre-forming the catalyst in toluene at reflux before adding the reagents has proven successful in more difficult transformations.<sup>7</sup> This approach was adopted and the amine component was added after 30 minutes reaction time in order to allow the catalyst and ligand to form the active isomerisation species and to allow the isomerisation step to begin turning over without possible hindrance by the amine. The results of the catalyst loading screen using 1-phenyl-pent-2-yne-1,4-diol **44** as the model substrate (**Scheme 68**) can be seen in **Table 10**.



**Scheme 68.**  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** and xantphos **58** catalyst loading screen.

Entry <sup>a</sup>	Catalyst/ligand loading (mol %)	Conversion (%) <sup>b</sup>	46 (%) <sup>b</sup>	47 (%) <sup>b</sup>	99 (%) <sup>b</sup>
1	1	70	18	12	40
2	2.5	100	25	9	66
3	5	100	10	22	68

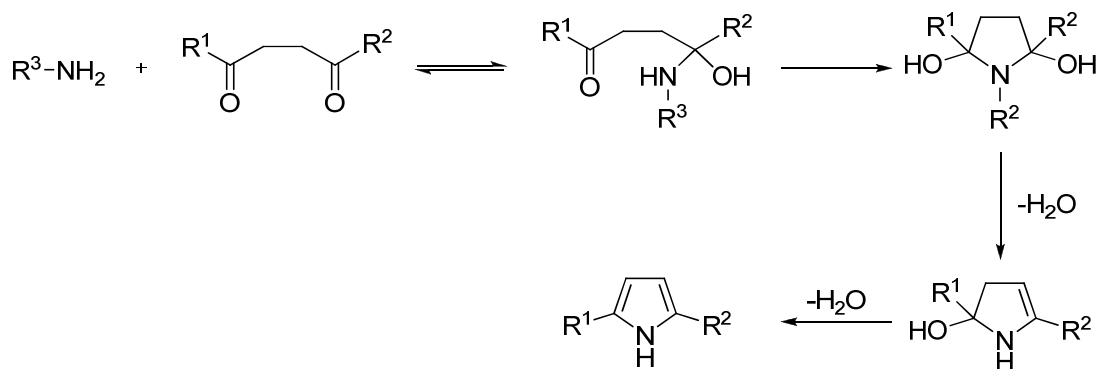
<sup>a</sup> Reactions carried out on 1mmol scale. Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55** and xantphos **58** was heated in toluene at reflux for 30 min in the presence of 1-phenyl-pent-2-yne-1,4-diol **44**. Benzylamine (1 equivalent) was then added and the reaction reflux in toluene for a total of 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis.

**Table 10.** Results of catalyst loading screen.

By pre-forming the catalyst in toluene at reflux we can see an immediate improvement in product distribution. With 1 mol% catalyst loading we can confirm what we found during the initial studies that pyrrole formation from 1,4-alkyne diols is a more challenging process than for the furan chemistry. Using 2.5 mol% catalyst loading the best distribution of products was achieved. Using 5 mol% catalyst loading we can confirm that the yield of furan side product is increased due to possible condensation of the 1,4-diketone catalysed by the ruthenium acting as a Lewis acid making 5 mol% catalyst excessive and unnecessary. Catalyst loading of 2.5 mol% gave the lowest furan side product formation and gave 100% conversion of starting material **44** to 1,4-diketone **46**. By altering the concentration of amine required for the reaction the yield of pyrrole could be increased.

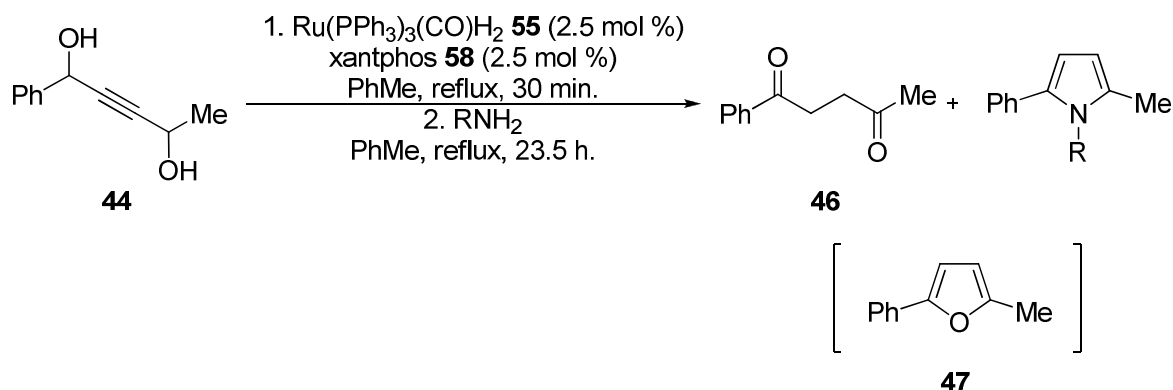
### 3.5 Amine Loading Screen

Extensive NMR studies by Amarnath and Amarnath<sup>8</sup> show that the mechanism for nucleophilic attack of an amine to a 1,4-diketone is much more complex than that for the acid catalysed cyclisation of furans. The most commonly accepted and general mechanism is outlined in (**Scheme 69**).



**Scheme 69.** General mechanism for pyrrole formation from 1,4-diketones.

Simplified, the intermediate hemiaminal undergoing cyclisation is the rate determining step. The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at  $\text{pH} < 3$  led to furans as main products. The basicity of the amine component can influence the rate and indeed at a high pH, formation of pyrrole is accelerated.<sup>9</sup> In accordance with observations by Katritzky<sup>10</sup> and Zeng<sup>9</sup> substitution at the 2-position and more importantly the 1-position on the amine reduced the rate of reaction. Using benzylamine and 2-phenethylamine ( $\text{pK}_a$  9.78 and 9.34 respectively)<sup>11,12</sup> we felt that the criteria to effect substantial pyrrole formation would be fulfilled. A screen of concentration using these two amines was conducted. (**Scheme 70, Table 11**).



**Scheme 70.** Amine loading screen

Entry <sup>a</sup>	Amine	Equiv.	Conversion <sup>b</sup> (%)	46 (%) <sup>b</sup>	47 (%) <sup>b</sup>	Pyrrole (%) <sup>b</sup>
1	Benzylamine	1	100	16	7	77
2	2-Phenethylamine	1	100	27	3	70
3	Benzylamine	2	100	10	6	84
4	2-Phenethylamine	2	100	11	4	85
5	Benzylamine	3	90	14	3	73
6	2-Phenethylamine	3	89	8	6	75

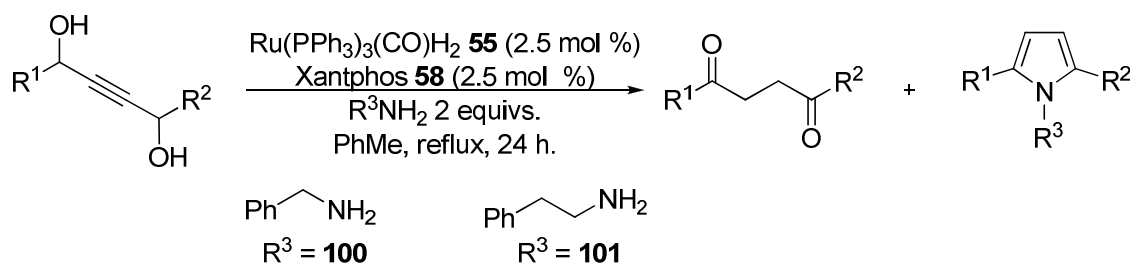
<sup>a</sup> Reactions carried out on 1mmol scale. Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> and xantphos was reflux in toluene for 30 min in the presence of 1-phenyl-pent-2-yne-1,4-diol **44**. Benzylamine or 2-phenethylamine was added in indicated equivalents and the reaction was refluxed in toluene for a total of 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis.

**Table 11.** Results of amine loading screen.

There seemed to be little difference between using benzylamine or 2-phenethylamine which was expected as they are both similarly nucleophilic, and both are unbranched primary amines. Using one equivalent of amine gave results similar to what we saw previously with the initial studies and catalyst loading investigation. 100% conversion was achieved but showed lower pyrrole formation, 77% and 70% respectively and with high quantities of 1,4-diketone **46** remaining (**Table 11, entries 1 and 2**). Using two equivalents of amine give excellent product distribution and both benzylamine and 2-phenethylamine gave similar result yielding 84% and 85% pyrrole with only 10-11% 1,4-diketone remaining with low furan side product being formed (**Table 11, entries 3 and 4**). As expected, using three equivalents of amine did not favour the cyclisation step over any possible inhibiting of the initial isomerisation step.

### 3.6 Synthesis of *N*-2,5-Trisubstituted Pyrroles.

Using 2 equivalents of amine nucleophile after pre-forming the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$ /xantphos active catalytic species in toluene at reflux for 30 minutes would allow us to synthesise a range of *N*-2,5-disubstituted pyrroles. By altering the 1,4-alkyne diol starting material we can manipulate the nature of the 2,5-substitution pattern and using benzylamine and 2-phenethylamine in these cases to become the component of the *N*-substitution. Similarly by altering the amine the *N*-substitution component can be manipulated. A range of 1,4-alkyne diols (**Scheme 71**) were subjected to the reaction conditions and the results are shown in **Table 12**.



**Scheme 71.** Synthesis of various *N*-2,5-disubstituted pyrroles.

Entry <sup>a</sup>	1,4-Alkyne diol	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. (%) <sup>b</sup>	Ketone (%) <sup>b</sup>	Furan (%) <sup>b</sup>	Pyrrole (%) <sup>b</sup>
1	<b>41</b>	Me	Me	<b>100</b>	100	0	0	100 (76) <sup>c</sup>
2	<b>61</b>	Me	<sup>i</sup> Pr	<b>100</b>	100	0	10	90
3	<b>41</b>	Me	Me	<b>101</b>	100	0	0	100 (84) <sup>c</sup>
4	<b>60</b>	Me	<sup>n</sup> Pr	<b>101</b>	100	0	14	86
5	<b>61</b>	Me	<sup>i</sup> Pr	<b>101</b>	100	0	35	65
6	<b>63</b>	Me	CH <sub>2</sub> CH <sub>2</sub> Ph	<b>101</b>	100	0	29	71
7	<b>44</b>	Me	Ph	<b>101</b>	100	4	12	84 (41) <sup>c</sup>
8	<b>71</b>	Me	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>101</b>	100	16	13	71
9	<b>72</b>	Me	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>101</b>	100	9	25	66
10	<b>102</b>	Me	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>101</b>	100	1	29	70
11	<b>73</b>	Me	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	<b>101</b>	100	0	9	91
12	<b>74</b>	Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>101</b>	100	30	25	0
13	<b>76</b>	Me	Naphthyl-	<b>101</b>	100	20	10	70
14	<b>77</b>	Me	2-Furyl-	<b>101</b>	100	0	14	86

<sup>a</sup> Reactions carried out on 1mmol scale. 1,4-Alkyne diol and Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (2.5 mol %) and xantphos (2.5 mol %) were dissolved in PhMe and heated to reflux. After 30 mins 2 equivalents of amine (2 mmol) was added to the reaction. Heating at reflux continued for a total of 24 hours. After 24 hours the reaction was cooled, diluted with MeOH:PhMe (1:1) and analysed by GC-MS without further purification. <sup>b</sup> Determined by GC-MS analysis. <sup>c</sup> Yields in parentheses are isolated yields after column chromatography. Many compounds were unstable to chromatography. Compound numbers run from **103** for **entry 1** to **116** for **entry 14**.

**Table 12.** Formation of pyrroles from various 1,4-alkyne diols and benzylamine or 2-phenethylamine.

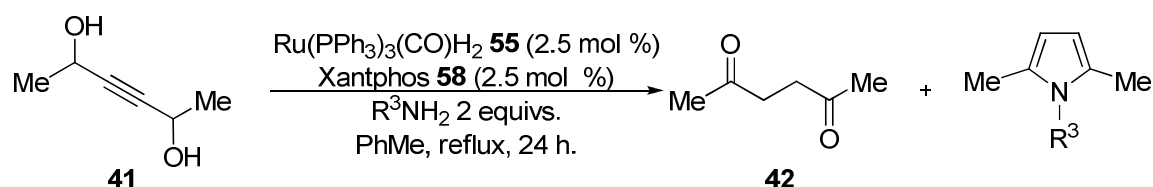
The reactions shown in **Table 12** were highly selective for pyrrole formation when unhindered substrates were used. (**Table 12 entry 1 to 4**). The use of more hindered substrates still afforded pyrroles selectively although in some cases showed significant furan side product formation (due to the more difficult cyclisation conditions shown in **Table 12 entries 5 and 6**). The 1,4-alkyne diol containing a *t*-butyl group **66** showed no conversion to pyrrole. Similarly the 1,4-alkyne diol **69** containing an *ortho*-bromine also showed no conversion to pyrrole. These results were expected due to either the bulky



substituents hindering the initial nucleophilic attack of the amine or cyclisation of the resulting hemiaminal. Positively, many functional groups were tolerated, including halide, nitrile and furyl.

### 3.7 Synthesis of *N*-2,5-Substituted Pyrroles: Amine Scope

Investigating the nature of the amine that could be used in this reaction was important to allow for manipulation of the *N*-substituent. Using 3-hexyne-2,5-diol **41** as the model substrate, a variety of amines were investigated in order to synthesise a variety of differently *N*-substituted 2,5-dimethyl pyrroles (**Scheme 72**, **Table 13**).



**Scheme 72.** Screen of various amines.

Entry <sup>a</sup>	$R^3NH_2$	Conv. (%) <sup>b</sup>	<b>42</b> (%) <sup>b</sup>	Furan (%) <sup>b</sup>	Pyrrole (%) <sup>b</sup>	Compound $N^o$
1	Aniline <b>117</b>	100	22	2	76 (63) <sup>c</sup>	<b>123</b>
2	4-Chloroaniline <b>118</b>	100	28	0	72 (69) <sup>c</sup>	<b>124</b>
3	4-Nitroaniline <b>119</b>	100	83	17	0	<b>n/a</b>
4	4-Methoxyaniline <b>120</b>	100	2	0	98 (61) <sup>c</sup>	<b>125</b>
5	Benzylamine <b>100</b>	100	0	0	100 (76) <sup>c</sup>	<b>103</b>
6	2-Phenethylamine <b>101</b>	100	0	0	100 (84) <sup>c</sup>	<b>104</b>
7	1-Phenethylamine <b>121</b>	100	1	0	99 (54) <sup>c</sup>	<b>126</b>
8	2-Aminopyridine <b>122</b>	100	63	4	33	<b>127</b>

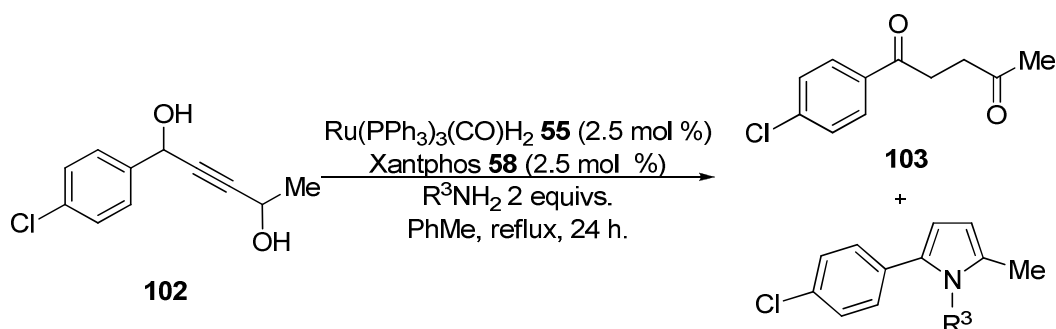
<sup>a</sup> Reactions carried out on 1 mmol scale. 1,4-Alkyndiol and  $Ru(PPh_3)_3(CO)H_2$  (2.5 mol %) and xantphos (2.5 mol %) were dissolved in PhMe and heated to reflux. After 30 min 2 equivalents of amine (2 mmol) was added to the reaction. Heating at reflux continued for a total of 24 hours. After 24 hours the reaction was cooled, diluted with MeOH:PhMe (1:1) and analysed by GC-MS without further purification. <sup>b</sup> Determined by GC-MS analysis. <sup>c</sup> Yields in parentheses are isolated yields after column chromatography.

**Table 13.** Results of using various amines to synthesise pyrroles from 1,4-alkyne diols.

We were pleased to find that aniline could be used as the nucleophile (**Table 13, entry 1**) in this system which overcomes the disadvantages of Watanabe's system.<sup>4</sup> Although some diketone did remain uncyclised under these conditions, reflecting the poor nucleophilicity of anilines with respect to aliphatic amines. The 4-nitroaniline (**Table 13, entry 3**) being a very poor nucleophile due to the presence of the strongly electron withdrawing *para*-nitro functionality produced no pyrrole product. Conversely, 4-methoxyaniline with the electron donating *para*-methoxy group reacted with excellent selectivity to pyrrole, 98% in this case (**Table 13, entry 4**). An amine with a substituent in the alpha-position was also successful (**Table 13 entry 7**). However, 2-aminopyridine (**Table 13, entry 8**) was a problematic amine giving unsatisfactory conversion of pyrroles under these reaction conditions.

### 3.8 Synthesis of *N*-2,5-Substituted Pyrroles: Amine Scope II

Changing the amine component in the reaction for unhindered substrates such as the dimethyl 1,4-alkyne diol showed favourable results for the majority of aliphatic amines and anilines. 2-(*p*-Chloro)-substituted 1,4-alkyne diol **103**, which when used in conjunction with 2-phenethylamine, gave 100% conversion with 1% 1,4-diketone remaining, 29% furan and 70% pyrrole product (**Table 12, entry 10**). Therefore we felt that using 2-(*p*-chloro)-substituted 1,4-alkyne diol **102** with various amines and anilines will give a good comparison of the various amines and anilines ability to afford cyclisation (**Scheme 73, Table 14**).



**Scheme 73.** Reaction of various amines with -(*p*-chloro)-substituted 1,4-alkyne diol **103**

Entry <sup>a</sup>	R <sup>3</sup> NH <sub>2</sub>	Conv. (%) <sup>b</sup>	104 (%) <sup>b</sup>	Furan (%) <sup>b</sup>	Pyrrole (%) <sup>b</sup>	Compound N <sup>o</sup>
1	Aniline <b>117</b>	100	22	2	33	<b>128</b>
2	4-Chloroaniline <b>118</b>	100	28	0	19	<b>129</b>
3	4-Methoxyaniline <b>120</b>	100	0	50	50	<b>130</b>
4	Benzylamine <b>100</b>	100	1	29	70	<b>131</b>
5	2-Phenethylamine <b>101</b>	100	1	29	70	<b>112</b>
6	1-Phenethylamine <b>121</b>	100	0	33	67	<b>132</b>
7	2-Aminopyridine <b>122</b>	100	42	56	2	<b>133</b>
8	1-Aminopentane <b>123</b>	100	0	45	55	<b>134</b>
9	<i>Iso</i> -Propylamine <b>124</b>	100	14	59	27	<b>135</b>
10	Benzamide <b>125</b>	65	15	50	0	n/a

<sup>a</sup> Reactions carried out on 1 mmol scale. 1,4-Alkynediol and Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (2.5 mol %) and xantphos (2.5 mol %) were dissolved in PhMe and heated to reflux. After 30 min 2 equivalents of amine (2 mmol) was added to the reaction. Heating at reflux continued for a total of 24 hours. After 24 hours the reaction was cooled, diluted with MeOH:PhMe (1:1) and analysed by GC-MS without further purification. <sup>b</sup> Determined by GC-MS analysis.

**Table 14.** Formation of pyrroles from 1,4-Alkyne diol **102** and various amines.

Using 1,4-Alkyne diol **102** conversions to pyrrole were as expected slightly lower. The most favourable conversions were found using unbranched aliphatic primary amines (**Table 14**, entries **5**, **6** and **8**). The use of the branched aliphatic amine  $\alpha$ -methylbenzylamine provided acceptable conversion of 67% pyrrole but is not as satisfactory as when used with the less hindered dimethyl 1,4-alkynediol **41**. In the case of *iso*-propylamine the conversion was very low but could be attributed to an issue of volatility (b.p. 34 °C) (**Table 14**, entry **10**). The use of anilines with the chloro-containing alkyne diol provided the best selectivity of 50% in the case of the electron rich 4-methoxyaniline (**Table 14** entry **3**). Benzamide was found to be unreactive towards pyrrole formation (**Table 14**, entry **11**). These findings emphasise the steric hindrance encountered by certain amines when combined with the bulkier 1,4-alkyne diols.

### 3.9 Chapter Summary

- Used the isomerisation reaction combined with addition of 2 equivalents of amine nucleophile to produce *N*-2,5-disubstituted pyrroles using 1,4-alkyne diols as 1,4-diketone surrogates.
- Using various 1,4-alkyne diols a range of different *N*-benzyl and *N*-phenethyl 2,5-disubstituted pyrroles were synthesised.
- A variety of different amines were used in conjunction with selected substrates to synthesis a range of differently *N*-substituted pyrroles.
- Overall an efficient system to synthesis a range of various pyrroles using various 1,4-alkynediols and amines has been achieved.
- The results of this study have been published.<sup>13</sup>

### 3.10 References

1. Tsuji, Y.; Huh, K. T.; Ohsugi, Y.; Watanabe, Y., *J. Org. Chem* **1985**, *50*, 1365.
2. Abbenhuis, R.; Boersma, J.; van Koten, G., *J. Org. Chem.* **1998**, *63*, 4282.
3. Hamid, M.; Williams, J. M. J., *Chem. Commun.* **2007**, 725.
4. Tsuji, Y.; Yokoyama, Y.; Huh, K. T.; Watanabe, Y., *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456.
5. Chowdhury, R. L.; Backvall, J. E., *J. Chem. Soc.-Chem. Commun.* **1991**, 1063.
6. Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J., *Tetrahedron Lett.* **2006**, *47*, 6787.
7. Anand, N.; Owston, N. A.; Parker, A. J.; Slatford, P. A.; Williams, J. M. J., *Tetrahedron Lett* **2007**, *48*, 7761.
8. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G., *J. Org. Chem.* **1991**, *56*, 6924.
9. Zeng, G. Z.; Yan, J. S.; Shen, D. Z., *Acta. Chim. Sinica.* **1981**, *39*, 215.
10. Katritzky, A. R.; Yousaf, T. I.; Chen, B. C.; Zeng, G. Z., *Tetrahedron* **1986**, *42*, 623.
11. Hall, H. K. J., *J. Am. Chem. Soc* **1957**, *79*, 5441.
12. Tuckerman, M. M.; Meyer, J. R.; Nachod, F. C., *J. Am. Chem. Soc* **1959**, *81*, 92.
13. Pridmore, S. J.; Slatford, P. A.; Daniel, A.; Whittlesey, M. K.; Williams, J. M. J., *Tetrahedron Lett.* **2007**, *48*, 5115.

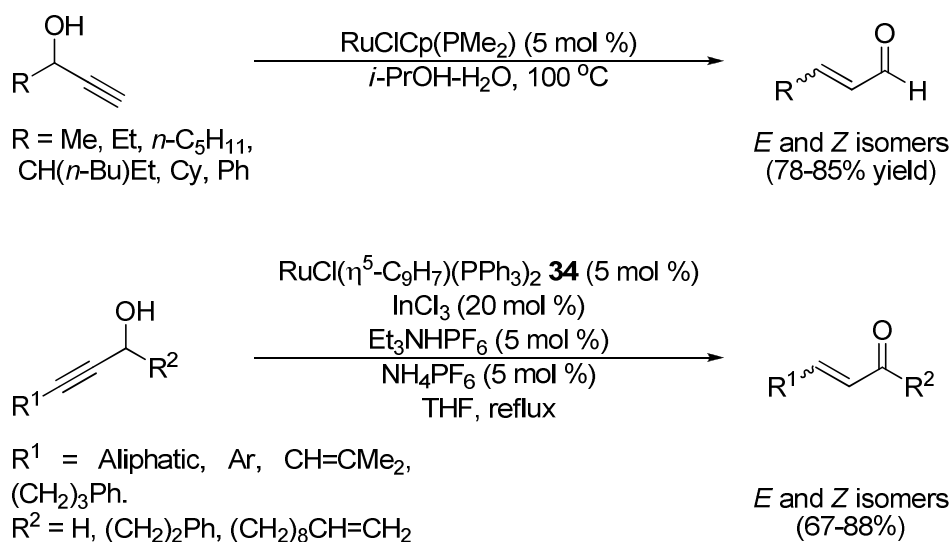
## 4 RESULTS AND DISCUSSION III

### 4.1 Aim

Use the established ruthenium xantphos catalyst system to isomerise propargylic alcohols into  $\alpha,\beta$ -unsaturated aldehydes with subsequent reaction with a suitable nucleophile to afford  $\alpha,\beta$ -unsaturated ester and acid derivatives.

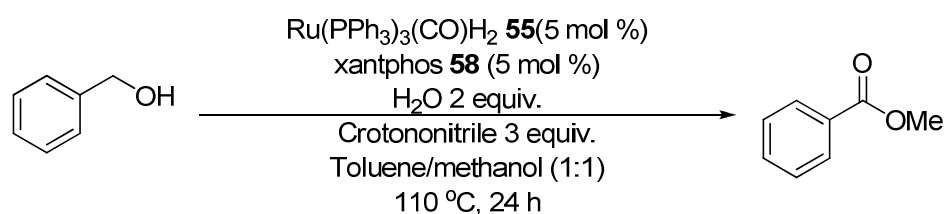
### 4.2 Background

Ruthenium compounds are known to facilitate Meyer-Schuster, Rupe and redox type rearrangements of various propargylic alcohols (*vide supra*) (Scheme 74).<sup>1-4</sup>



**Scheme 74.** Examples of ruthenium catalysed isomerisations of propargylic alcohols.

With the possibility of generating the  $\alpha,\beta$ -unsaturated aldehydes *in situ* said aldehydes could be reacted with a suitable nucleophile such as methanol *via* 1,2 addition. Previous work in the group has demonstrated that methanol has been used to oxidise alcohols to aldehydes and then to the corresponding methyl esters *via* a hemi-acetal intermediate using methanol as the nucleophile (Scheme 75).<sup>5</sup>



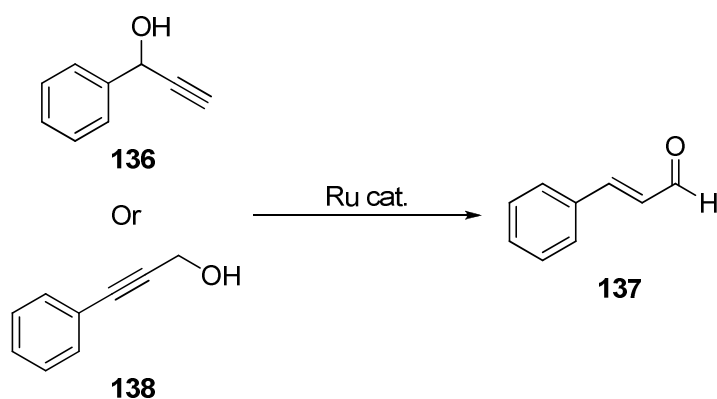
**Scheme 75.** Ruthenium catalysed oxidation of alcohols with methanol.

By combining both the ruthenium catalysed isomerisation and ruthenium catalysed oxidation of alcohols with methanol a novel route to  $\alpha,\beta$ -unsaturated methyl esters could be achieved.

### 4.3 Isomerisation of Propargylic Alcohols

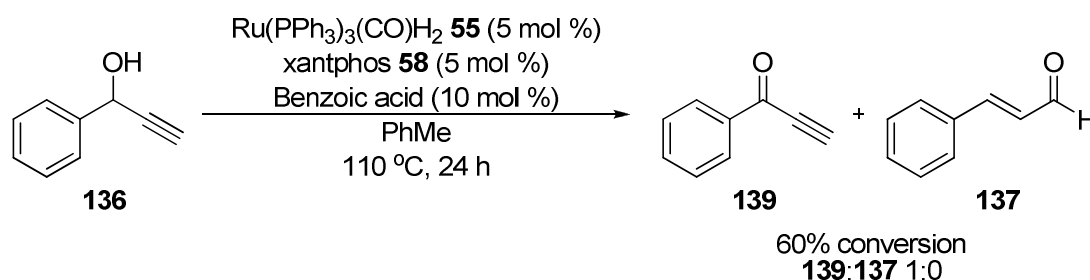
#### Initial studies

Initial studies focused on the rearrangement of two substrates. A secondary propargylic alcohol such as 1-phenyl-2-propyn-1-ol **136** could be isomerised *via* a Meyer-Schuster type rearrangement to afford the  $\alpha,\beta$ -unsaturated aldehyde; cinnamaldehyde **137**. A primary propargylic alcohol such as 3-phenyl-2-propyn-1-ol **138** could be isomerised *via* redox isomerisation to also afford cinnamaldehyde **137** (**Scheme 76**). Such reactions are well known in the literature (*vide supra*). Subsequently the  $\alpha,\beta$ -unsaturated acid or ester could be isolated or it could be reduced *in situ* to the alkane product.



**Scheme 76.** Proposed route to  $\alpha,\beta$ -unsaturated aldehydes from

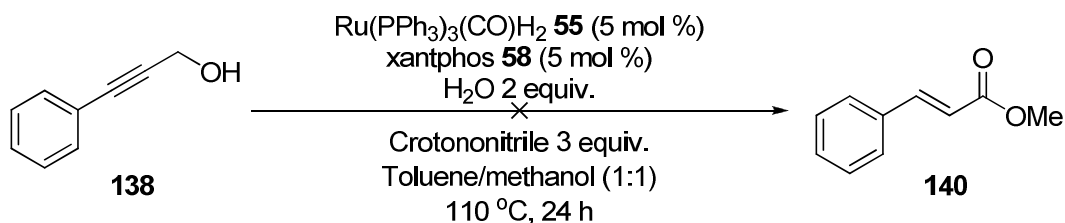
By combining the already established ruthenium xantphos complex catalysed isomerisation of 1,4-alkynediols and using methanol as a nucleophile a route to  $\alpha,\beta$ -unsaturated aldehydes should be possible. Initially the ability of the ruthenium xantphos systems to isomerise the propargylic alcohols; 1-phenyl-2-propyn-1-ol **136** and 3-phenyl-2-propyn-1-ol **138** were investigated (**Scheme 77**).



**Scheme 78.** Initial isomerisation investigation.

Using the ruthenium xantphos system at 5 mol % and with benzoic acid present to assist the Meyer-Schuster type rearrangement the 1-phenyl-2-propyn-1-ol substrate showed poor conversion. When examined by  $^1\text{H}$  NMR analysis the conversion was solely to oxidation of the starting material to the 1-phenyl-2-propyn-1-one **139**, probably due to loss of molecular hydrogen *via* acceptor-less transfer hydrogenation. There was no trace of cinnamaldehyde **137** by  $^1\text{H}$  NMR analysis. Similarly in the planned redox isomerisation of 3-phenyl-2-propyn-1-ol **138** with the ruthenium xantphos system there was no conversion of starting materials to product. The cinnamaldehyde **137** product could prove to be too reactive in these cases and loss of product could have happened through decarbonylation.<sup>6</sup> This was notably observed by de Vries when using  $\text{Ru(PPh}_3)_4\text{H}_2$  with cinnamaldehyde **137** which also deactivated the catalyst.<sup>7</sup> Similarly the reversibility of competing transfer hydrogenation reactions could also be hindering the reaction. By using the “all in one” reaction with methanol as a nucleophile we hoped that some methyl cinnamate **140** could be formed, with the methanol trapping the reactive aldehyde intermediate and impede any subsequent unwanted side reactions. (**Scheme 79**).





**Scheme 79.** “One-pot” route to  $\alpha,\beta$ -unsaturated esters from propargylic alcohols.

Unfortunately reaction was observed with no formation of methyl cinnamate **140** and with no conversion of starting material. The isomerisation of propargylic alcohols to the requisite  $\alpha,\beta$ -unsaturated aldehydes with subsequent nucleophilic attack with methanol, for example, seemed to be an unlikely process to be developed further. The initial isomerisation step failed in both examples thus hindering any further reaction in the proposed cascade system. Even if the reaction was optimised we felt that the starting propargylic alcohols, due to their limited availability would hinder the diversity of the system. It was decided to investigate another route to the desired target  $\alpha,\beta$ -unsaturated esters.

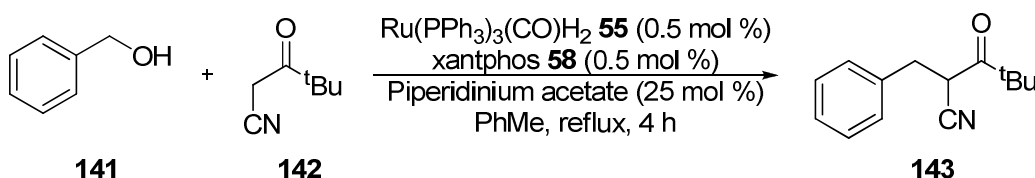
#### 4.4 Alkenes from Alcohols.

#### 4.5 Aim

Our aim was to develop a tandem hydrogen transfer and Knoevenagel condensation as an alternative route to  $\alpha,\beta$ -unsaturated ester from alcohols. Double homologation of alcohols to esters would also be investigated by using the “borrowing hydrogen” methodology.

#### 4.6 Background

Previous research in the Williams group had demonstrated that malonate type nucleophiles could be used to form C-C bonds from alcohols<sup>8</sup> *via* “borrowing hydrogen” (Scheme 80).<sup>8</sup>

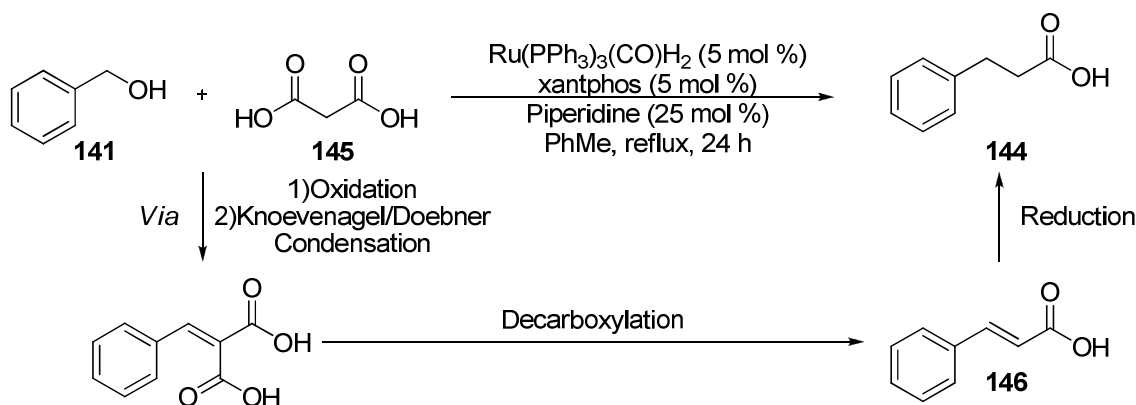


**Scheme 80.** “Borrowing hydrogen” in the Knoevenagel condensation of alcohols.

This system, with the oxidation of benzyl alcohol **141**, allowed subsequent nucleophilic attack of ketonitrile **142**, to form the  $\alpha,\beta$ -unsaturated Knoevenagel product *via* the traditional Knoevenagel condensation. The alkene formed is then reduced by the hydrogen taken from the alcohol in the initial step to form **143**. Other malonate type compounds were used such as dibenzyl malonate and ethyl cyanoacetate but required a much higher catalyst loading at 5 mol % and longer reaction times, typically 24 hours.

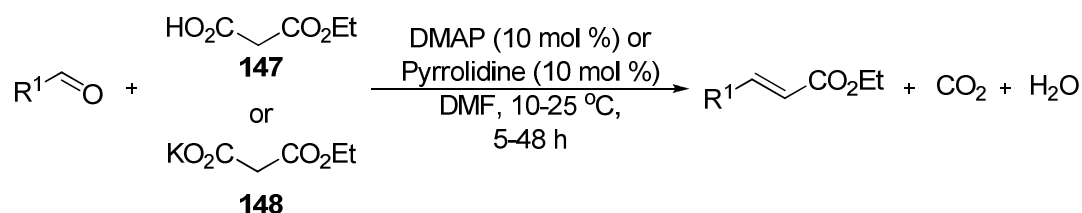
In the pursuit of exploiting the Knoevenagel condensation coupled with ruthenium catalysed oxidation of alcohols we were interested in firstly synthesising dihydrocinnamic acid **144** from the reaction between benzyl alcohol **141** and malonic acid **145**. It was hoped that the reaction would proceed *via* the Doebner modification under the right conditions resulting in a decarboxylative reaction followed by reduction

of **146** from the “borrowed hydrogen” from the initial step, resulting in the dihydrocinnamic acid **144** product (**Scheme 81**).



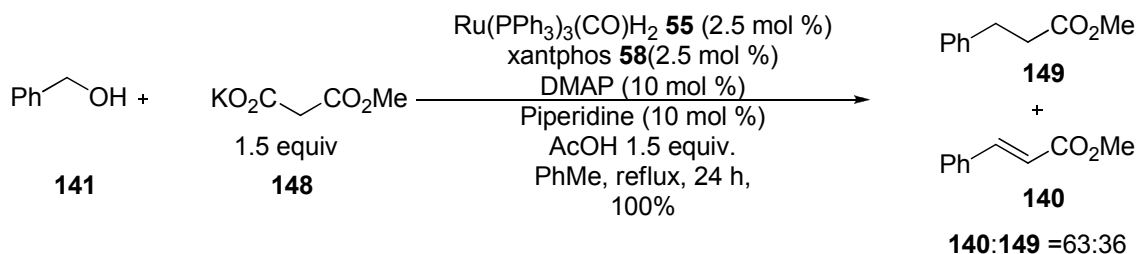
**Scheme 81.** Initial route to dihydrocinnamic acid **144**

The  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  (5 mol %) and xantphos (5 mol %) system with piperidine as co-catalyst, that was successful for the previous Knoevenagel type reaction of alcohols was applied to oxidise benzyl alcohol **141** in the presence on malonic acid **145**. The initial result showed both very poor conversion 44% with little product formation, 10%, with the majority of the product being benzaldehyde. With the classical Knoevenagel-Doebner reaction carried out in pyridine at reflux it was felt that the use of piperidine was a poor base to catalyse this transformation. The base should both be able to cause the deprotonation to allow decarboxylation to the  $\alpha,\beta$ -unsaturated product or/and be able to form the enolate of the malonic acid or enhance the electrophilicity of the aldehyde by formation of the iminium species. Also the malonic acid itself could be decarboxylating *in situ* this has been observed in transition metal systems resulting in acetic acid and carbon dioxide.<sup>9</sup> List and co-workers<sup>10, 11</sup> recently reported the conversion of aldehydes into unsaturated esters using a decarboxylative condensation of malonate half esters **147** and their salts **148** (**Scheme 82**).



**Scheme 82.** List's decarboxylative condensation of malonate half esters.

By replacing malonic acid with malonate half esters **147**, and the corresponding potassium salts **148**, it was anticipated that coupling this reaction with the ruthenium catalysed “borrowing hydrogen” the conversion would be greatly improved along with greater throughput to the alkene and alkane products. When using the potassium half malonate salt an equivalent of acetic acid is added to reprotonate the salt *in situ*. The  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** (2.5 mol %) and xantphos **58** (2.5 mol %) were combined with the conditions reported by List *et al.* in an attempt to alkylate benzyl alcohol **141** with potassium methyl malonate **148** (**Scheme 83**).



**Scheme 83.** Initial reaction using malonate half ester salts.

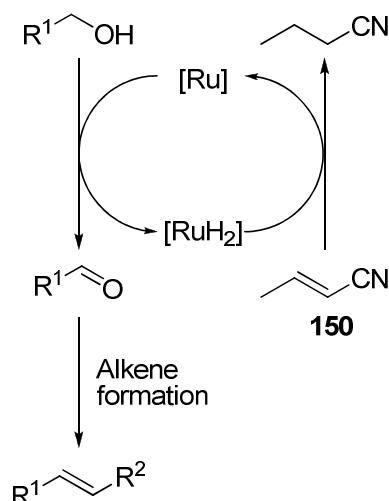
At this stage noticing the distribution of alkane **149** and alkene **140** (63:36) products we decided to utilise a sacrificial hydrogen acceptor. This would be beneficial in three ways, firstly allowing us to perfect the condensation step without relying on the slow hydrogen transfer cycle to oxidise the alcohol using the cinnamate **140** as the hydrogen acceptor, and secondly this would allow us access to the alkene product which would then allow study and optimisation of the final reduction step. Finally, selective

formation of  $\alpha,\beta$ -unsaturated esters would be a useful methodology for other synthetic procedures.

#### 4.7 Optimisation

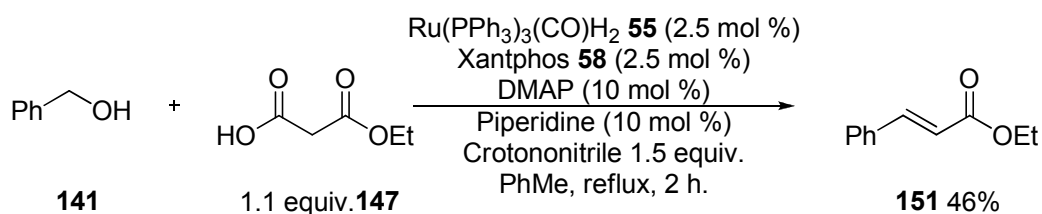
The Williams group recently reported that crotononitrile **150** is a useful hydrogen acceptor in the ruthenium catalysed oxidation of alcohols to methyl esters.<sup>5</sup> In the route to  $\alpha,\beta$ -unsaturated esters we were interested in the possibility of irreversibly oxidising alcohols using the crotononitrile **150** as a sacrificial acceptor for the hydrogen taken from the alcohol in the initial step. In order for this approach to be successful, the hydrogen acceptor must be able to accept the hydrogen more rapidly than the alkene is being formed, and the alkene forming reaction must not interfere with the hydrogen transfer. There are other examples of approaches to the conversion of alcohols to alkenes in the literature including oxidation with manganese dioxide and *in situ* Wittig reaction<sup>12</sup> along with sequential Swern/Wittig<sup>13</sup> and TPAP/Wittig<sup>14</sup> processes. Use of a catalytic oxidation systems with a subsequent Knoevenagel decarboxylative condensation could prove to be a useful and atom economic improvement on these earlier systems utilising stoichiometric oxidants along with the less atom efficient phosphorus ylide olefination reactions.

We proposed that using the combination of  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** with xantphos **58** we can irreversibly oxidise the alcohol with crotononitrile **150**. We can then perform the alkene formation step using the decarboxylative Knoevenagel condensation to selectively synthesise  $\alpha,\beta$ -unsaturated esters from alcohols (**Scheme 84**).



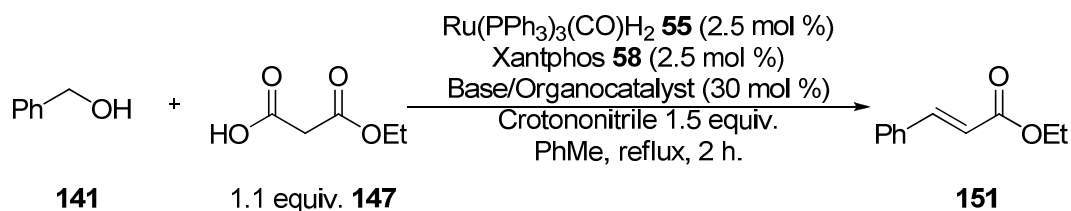
**Scheme 84.** Proposed ruthenium catalyzed formation of  $\alpha,\beta$ -unsaturated esters

A model reaction, with mono-ethyl malonate **147** and benzyl alcohol **141** was carried out coupling the system reported by List *et al.*<sup>11</sup> and the ruthenium xantphos combination, with 1.5 equivalents of crotononitrile **150** as the oxidant/hydrogen acceptor (**Scheme 85**).



**Scheme 85.** Model reaction for tandem hydrogen transfer and condensation.

The initial reaction outlined in **Scheme 85** was analysed after two hours by  $^1\text{H}$  NMR and gratifyingly showed 100% conversion with 46% ethyl cinnamate **151** formation with 54% remaining benzaldehyde. As the oxidation of benzyl alcohol **141** was complete within two hours, it was concluded that the Knoevenagel condensation step was the limiting factor in the formation of the  $\alpha,\beta$ -unsaturated ester **151**. Using the model reaction parameters a screen of bases and organo-catalysts was conducted (**Scheme 86**, **Table 15**).



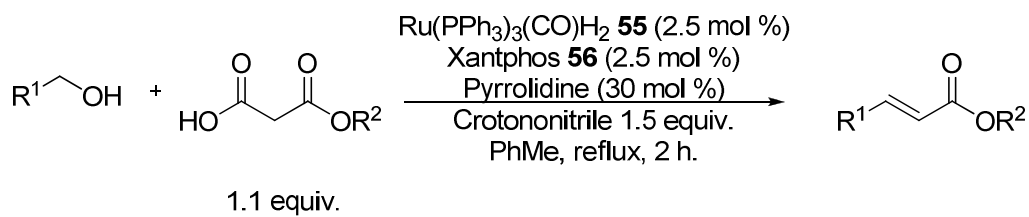
Scheme 86. Screening of base/organocatalyst co-catalysts.

Entry <sup>a</sup>	Base/Organocatalyst	Conversion (%) <sup>b</sup>	Benzaldehyde (%) <sup>b</sup>	Alkene 151 (%) <sup>b</sup>
1	Et <sub>3</sub> N	59	43	16
2	DMAP	69	56	13
3	Piperidinium acetate	84	21	63
4	Piperidine	100	18	82
5	Pyrrolidine	100	13	97

<sup>a</sup> Reactions carried out on 2 mmol scale. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis.

Table 15. Results of base screen.

The use of triethylamine and dimethylaminopyridine (DMAP) as basic catalysts led to low conversion to product (16% and 13%), with the major product being benzaldehyde (43% and 56%). The mechanism by which these catalysts work is *via* the formation of the enolate of the mono ethyl malonate, the Hann-Lapworth mechanism.<sup>15, 16</sup> Using secondary amines and their salts which go *via* an iminium mechanism with the benzaldehyde showed markedly improved reactivity.<sup>15, 17</sup> Piperidinium acetate as co-catalyst gave 84% conversion with 63% alkene **151** formation. However, piperidine and pyrrolidine gave the most favourable results with pyrrolidine standing out with 100% conversion of starting materials and 97% alkene **151** formation. Application of the outlined conditions to a range of alcohols and mono substituted malonates allowed us to synthesise a range of alkenes (Scheme 87, Table 16).

**4.8 Synthesis of alkenes from alcohols by tandem hydrogen transfer and condensation.****Scheme 87.** Optimised reaction conditions for forming alkenes from alcohols.



Entry <sup>a</sup>	Alkene product	Compound N <sup>o</sup>	Yield (%) <sup>b</sup>
1		<b>140</b>	74 <sup>c</sup>
2		<b>151</b>	95
3		<b>151</b>	71 <sup>c</sup>
4		<b>152</b>	84
5		<b>153</b>	71
6		<b>154</b>	87
7		<b>155</b>	90
8		<b>156</b>	74
9		<b>157</b>	71
10		<b>158</b>	83
11		<b>159</b>	74
12		<b>160</b>	73

<sup>a</sup> Reactions carried out on 4 mmol scale. <sup>b</sup> All reactions had reached full conversion as determined by the <sup>1</sup>H NMR spectrum of the crude reaction mixture which showed only the presence of the (*E*)-isomer of alkene. Isolated yields after column chromatography. <sup>c</sup> The potassium carboxylate salt of the malonate was used, with 1.5 equivalent of acetic acid used.

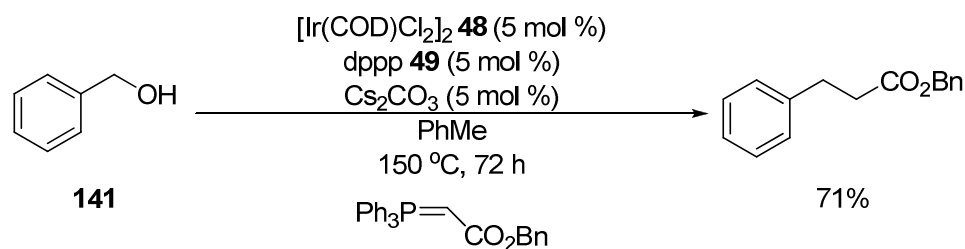
**Table 16.** alkenes synthesised by tandem oxidation/decarboxylative condensation.

Methyl, ethyl and *tert*-butyl esters were all formed with good isolated yields. The carboxylate salts could also be used in place of the half esters (**Table 16, entries 1 and 3**) with the addition of acetic acid. The carboxylate salts of malonate half esters are often cheaper than the acids, and are readily prepared from the diesters by treatment with base.<sup>11, 18</sup>

A variety substituted benzyl alcohols could be used including halides (**Table 16, entries 6-8**), electron donating groups (**Table 16, entries 9 and 10**) and electron withdrawing groups (**Table 16, entry 11**) along with the *ortho* substituted product formed in **Table 16, entry 12**.

However, use of aliphatic alcohols led to a mixture of  $\alpha,\beta$ - and  $\beta,\gamma$ -alkene products. Mechanistic studies by Corey<sup>19, 20</sup> showed that tautomerisation of the alkene before the decarboxylation gives a dienolate whose protonation occurs irreversibly in the more reactive alpha position resulting in the more predominant generation of the  $\beta,\gamma$ -unsaturated esters. Screening of various bases and conditions would not allow us to selectively synthesis  $\alpha,\beta$ -unsaturated esters from aliphatic alcohols.

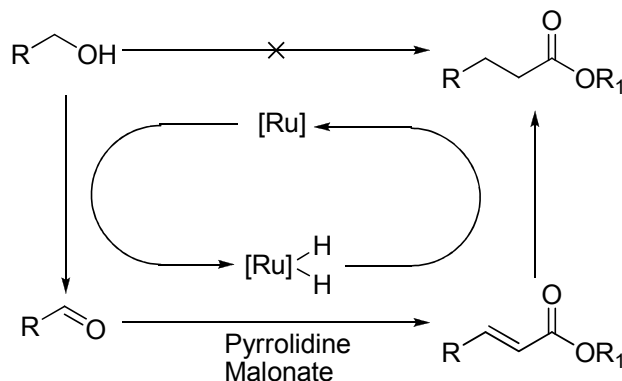
Using the system developed above (**Scheme 87**) it was envisioned that absence of the sacrificial hydrogen acceptor crotononitrile would allow us access to the alkane product from the decarboxylative Knoevenagel condensation. Previous work in the Williams group on the C-C bond formation from alcohols has focused on the Wittig and Horner-Wadsworth-Emmons reactions. (*vide supra*). These pioneering reactions however required long reaction times and high temperatures,<sup>21, 22</sup> and are inefficient with and equivalent of triphenylphosphine oxide being produced as waste (**Scheme 88**). We hoped to be able to improve these conditions to become more synthetically useful.



**Scheme 88.** Borrowing hydrogen in C-C bond formation from alcohols.

Using a ruthenium catalyst to oxidise the alcohol a decarboxylative Knoevenagel reaction, using the malonate mono esters, can take place on the resulting aldehyde. The

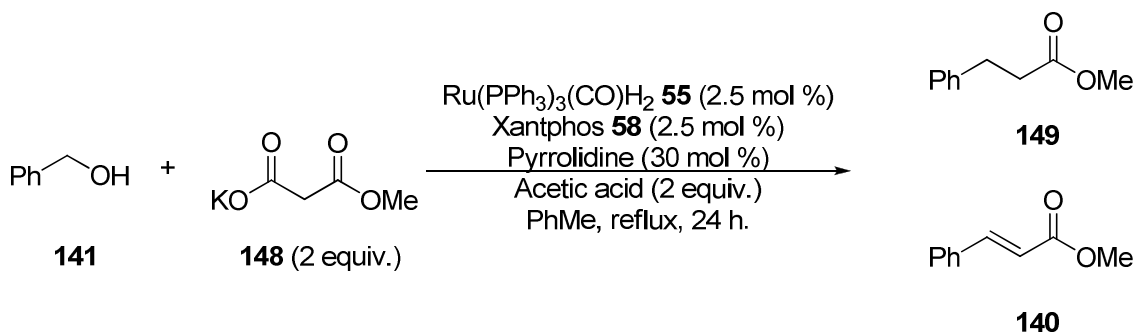
alkene formed with loss of water and carbon dioxide can then be reduced with the hydrogen taken from the initial oxidation reaction in a redox neutral process termed “borrowing hydrogen” (**Scheme 89**).



**Scheme 89.** “Borrowing hydrogen” in a route to alkanes from alcohols.

#### 4.9 Initial studies

Initial reactions conducted simply used the same conditions used in the synthesis of alkenes from alcohols with the absence of the sacrificial hydrogen acceptor, crotononitrile. The reaction time was increased in these cases to 24 hours due to the slower initial oxidation step being dependant on the formation of the alkene product. We also found that two equivalents of malonate nucleophile was needed to provide sufficient product formation (1.1 equivalents were used in the alkene chemistry), possibly due to competing decarboxylation of the starting materials and the slower nature of the transformation (**Scheme 90**).

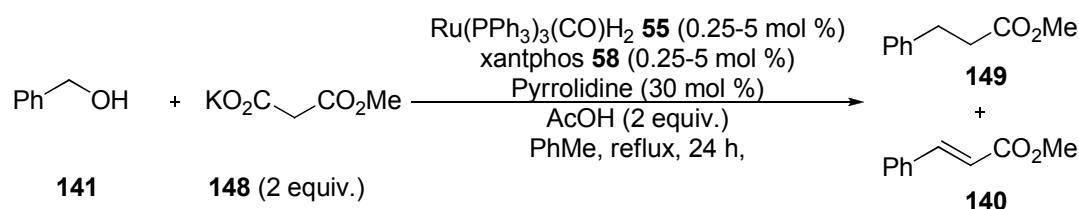


**Scheme 90.** Initial studies in alkane formation from alcohols

After repeating the reaction several times at the conditions demonstrated the reaction seemed to stop at around 90% conversion. The distribution of dihydromethylcinnamate **149** and methyl cinnamate **140** was around 6:3. It was envisioned that the initial ruthenium catalysed oxidation step was very rapid and the condensation of benzaldehyde with the half malonate **148** and subsequent decarboxylation was the rate limiting step. Subsequently there could be loss of molecular hydrogen from the alcohol and catalyst due to the slow formation of alkene **140** hindering conversions. After completion of the reaction at 24 h an equivalent of 2-propanol was added in order to attempt to push the conversion to product **149** further. This only seemed to reduce any remaining benzaldehyde back to benzyl alcohol, resulting in a conversion of 88% overall. Of this 79% was dihydromethylcinnamate **149** with 4% methyl cinnamate **140**. This indicates the ruthenium xantphos catalyst is either being deactivated after a certain amount of time, or that there is significant loss of hydrogen, which hinders further conversion (shown by reduction of benzaldehyde to benzyl alcohol) from the slow condensation-decarboxylation step.

#### 4.10 Optimisation

A screen of catalyst loading was conducted in order to optimise the reaction further. By varying the catalyst loading we envisaged optimisation of the product distribution (**Scheme 91**, **Table 17**).



Scheme 91. Catalyst loading screen.

Entry <sup>a</sup>	[Ru]/xantphos (mol %)	Conversion (%) <sup>b</sup>	<b>140</b> (%) <sup>b</sup>	<b>149</b> (%) <sup>b</sup>
1 <sup>c</sup>	0.25	94	14	67
2 <sup>c</sup>	0.5	86	19	52
3	1	94	14	67
4	2.5	88	15	74
5	5	87	19	67

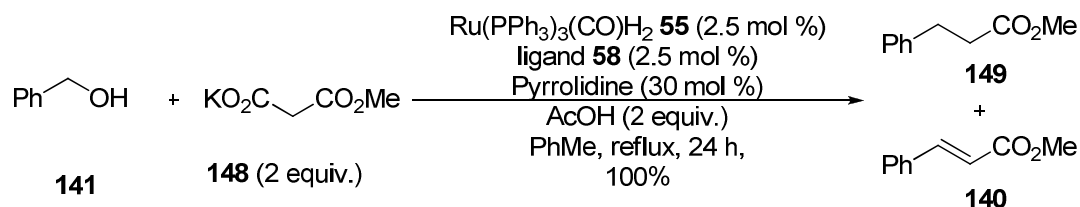
<sup>a</sup> Reactions carried out on a 2mmol scale. <sup>b</sup> Analysed by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> 48 h reaction time.

Table 17. Results of catalyst loading screen..

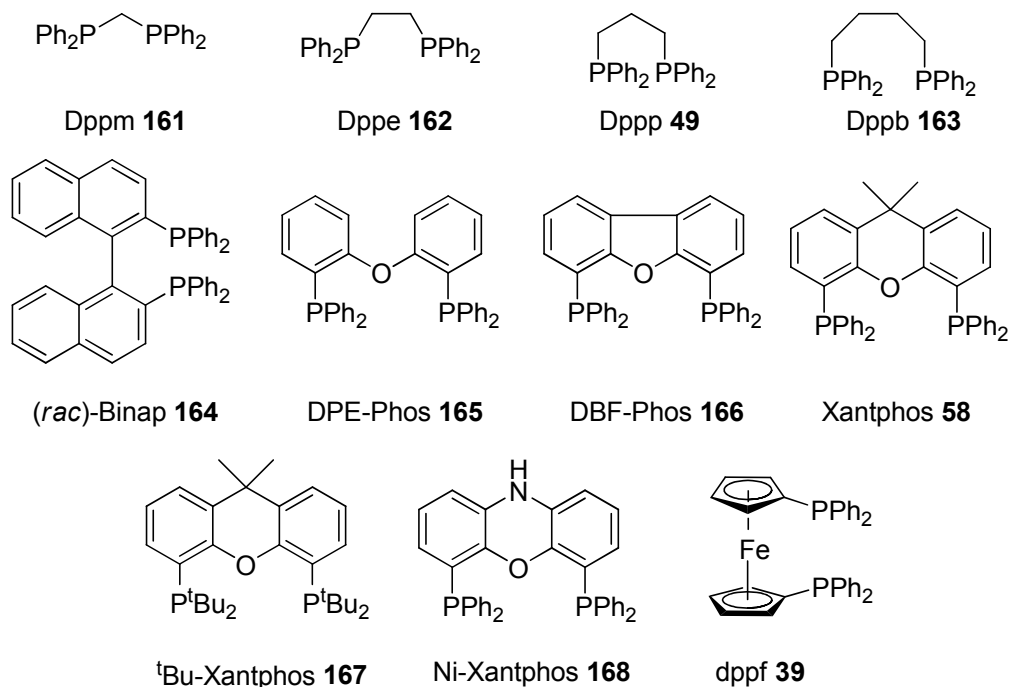
The reactions conducted in **Table 17** resulted with dihydromethylcinnamate **149** and methyl cinnamate **140** as the predominant products. The remainder of the reaction mixture consisted of unreacted benzyl alcohol. With the lower catalyst loadings a reaction time of 48 hours was needed in order to gain any useful level of conversion. After 24 hours conversion was less than 50% in the case of catalyst loading less the 1 mol%. There was a small amount of the benzyl ester formed from condensation of benzyl alcohol **141** with the potassium methyl malonate **148** but typically less than 5% in all cases. The catalyst loading had essentially no effect on the reaction conversion and using a catalyst and ligand loading of 2.5 mol % although has slightly lower conversions to alkane **149**, requires a shorter reaction time (24 h) and seemed preferential in alkylation of alcohols by “borrowing hydrogen”.

With the catalyst system being employed providing satisfactory conversion and results a ligand screen was conducted in order to improve the ruthenium catalyst ability to reduce

the  $\alpha,\beta$ -unsaturated ester more efficiently and rapidly as it is formed. A variety of bidentate phosphine ligands were investigated which have been shown to accelerate transfer hydrogenation reactions<sup>8</sup> (**Scheme 92**, **Table 18**).



**Scheme 92.** Ligand Screen.



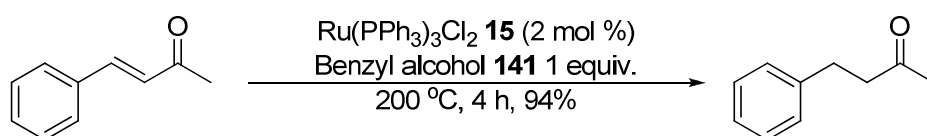
Entry <sup>a</sup>	Ligand	Conversion (%) <sup>b</sup>	140 (%) <sup>b</sup>	149 (%) <sup>b</sup>
1	None	15	2	1
2	Dppm <b>161</b>	15	2	0
3	Dppe <b>162</b>	22	6	4
4	Dppp <b>49</b>	35	22	0
5	Dppb <b>163</b>	50	30	8
6	( <i>Rac</i> )-Binap <b>164</b>	46	25	8
7	DPE-Phos <b>165</b>	44	24	8
8	DBF-Phos <b>166</b>	15	3	0
9	Xantphos <b>58</b>	75	10	52
10	<sup>t</sup> Bu-xantphos <b>167</b>	18	6	>1
11	Ni-xantphos <b>168</b>	0	0	0
12	Dppf <b>39</b>	67	30	26

<sup>a</sup> Reactions carried out on 2 mmol scale. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. Reactions consisted of a mixture of products **140** and **149** along with unreacted benzaldehyde and ester side product from reaction of benzyl alcohol with the half malonate.

Table 18. Results of the ligand screen.

Disappointingly there was no more efficient combination of using Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55** with any ligand other than xantphos **58**. A reaction time of 4 hours chosen in order to draw a direct comparison of reaction progress showed that the xantphos ligand was the best ligand to use in this system. The ferrocenyl species dppf showed good reactivity when combined with Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55** in the initial oxidation step but showed poor conversion of alkene to alkane. All the other bidentate ligands used conferred no benefit, including the other xantphos family of ligands **167** and **168** as well as the structurally analogous DPE-Phos **165** and DBF-Phos **166**.

Having optimised a system capable of synthesising alkanes from alcohols using a tandem hydrogen transfer Knoevenagel decarboxylative condensation, disappointingly we had to consider using an alternative ruthenium source, maybe even having to change to an iridium based catalyst. The use of ruthenium complexes to reduce  $\alpha,\beta$ -unsaturated compounds by transfer hydrogenation are extremely rare<sup>23</sup> in comparison to the analogous reduction of related olefins by numerous ruthenium complexes and molecular hydrogen. To date the  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** and  $\text{RuClH}(\text{PPh}_3)_3$  catalysts are the only ruthenium based system that have been used to reduce solely  $\alpha,\beta$ -unsaturated ketones and esters chemoselectively. The work conducted by Sasson and Blum<sup>24-26</sup> in the 1970's and early 80's and Cho's ruthenium catalysed transfer hydrogenation of ketones with alcohols accompanied by C-C coupling<sup>27</sup> (*vide supra*) is still the foremost method for reducing  $\alpha,\beta$ -unsaturated ketones and esters *via* hydrogen transfer. (**Scheme 93**)

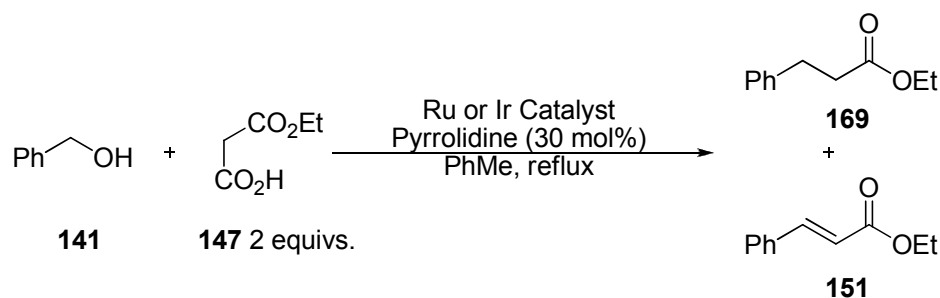


**Scheme 93.** Sasson's and Blum's reduction of  $\alpha,\beta$ -unsaturated ketones.

Using the  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15** catalyst, Bäckvall and co-workers found that addition of base to the transfer hydrogen reaction increased the rate of reaction markedly.<sup>28</sup> We hoped that by simply replacing the  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  **55** and xantphos **58** system with the  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  catalyst **15** (activated to the more reactive  $\text{RuH}_2(\text{PPh}_3)_3$  species by base *in situ*), we could perform the one-pot reaction to alkanes from alcohols with the already optimised Knoevenagel decarboxylative condensation step.

Fujita and Yamaguchi had used the  $[\text{Cp}^*\text{IrCl}_2]_2$  **50**/ $\text{Cs}_2\text{CO}_3$  catalyst system to good effect in various C-C and C-N bond forming reactions from alcohols.<sup>29</sup> We therefore, chose to compare the ruthenium xantphos system with Fujita and Yamaguchi's iridium based system and the  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2/\text{KOH}$  system following the literature procedures (**Scheme 94**, **Table 19**). For the decarboxylative Knoevenagel reaction the conditions optimised previously were used.





Scheme 94. Catalyst screen

Entry <sup>a</sup>	Catalyst <sup>b</sup>	Time (h)	Conversion (%) <sup>c</sup>	169 (%) <sup>c</sup>	151 (%) <sup>c</sup>
1	Ru(PPh <sub>3</sub> ) <sub>3</sub> (CO)H <sub>2</sub> <b>55</b> /xantphos <b>58</b>	24	100	62	38
2	Ru(PPh <sub>3</sub> )Cl <sub>2</sub> <b>15</b> /KOH	24	100	92	8
3	Ru(PPh <sub>3</sub> )Cl <sub>2</sub> <b>15</b> /KOH	4	93	82	11
4	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> <b>50</b> /Cs <sub>2</sub> CO <sub>3</sub>	24	100	100	0
5	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> <b>50</b> /Cs <sub>2</sub> CO <sub>3</sub>	4	79	76	3

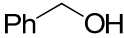
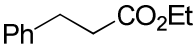
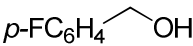
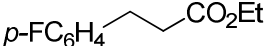
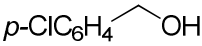
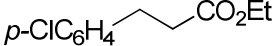
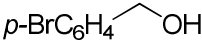
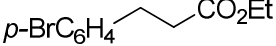
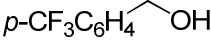
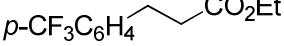
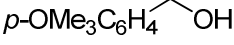
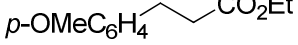
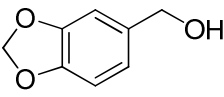
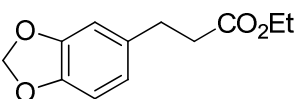
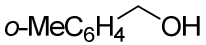
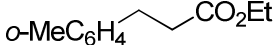
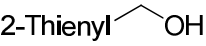
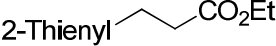
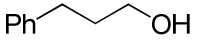
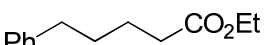
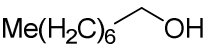
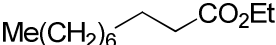
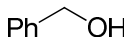
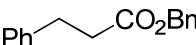
<sup>a</sup> Reactions carried out on 2 mmol scale. <sup>b</sup> Catalyst loading was 2.5 mol% (i.e. 2.5 mol% in Ru or 5 mol% Ir) KOH loading was 6.25 mol% and Cs<sub>2</sub>CO<sub>3</sub> 10 mol%. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis.

Table 19. Results of the catalyst screen.

Both the ruthenium systems still appear to suffer from possible hydrogen loss, however, the Ru(PPh<sub>3</sub>)Cl<sub>2</sub> **15**/KOH system gave a very favourable 92:8 ratio of alkane to alkene (Table 19, entry 2). Similarly the [Cp\*IrCl<sub>2</sub>]<sub>2</sub> **50**/Cs<sub>2</sub>CO<sub>3</sub> catalyst system gave a remarkable 100:0 alkane to alkene ratio (Table 19, entry 4). A comparison of the conversions between Ru(PPh<sub>3</sub>)Cl<sub>2</sub> **15**/KOH and [Cp\*IrCl<sub>2</sub>]<sub>2</sub> **50**/Cs<sub>2</sub>CO<sub>3</sub> after 4 hours showed that the ruthenium based system was slightly more active for this process (Table 19, entries 3 and 4). In combination with the fact that the effective catalyst loading was lower for the ruthenium system (2.5 mol % in ruthenium compared to 5 mol % in iridium) and the relative costs commercially of these complexes, the Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> **15**/KOH catalyst was chosen to perform the “borrowing hydrogen” cycle. In order to overcome the small problem of unreacted alkene and to assist in overcoming lengthy separation procedures, we found that adding isopropanol (20 mol %) to act as a

hydrogen donor to reduce any remaining alkene at the end of the reaction was beneficial. Using  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  **15**/KOH as the catalyst system a range of alcohols were converted into the doubly homologated ester derivatives (**Table 20**).

4.11 Synthesis of alkanes from alcohol *via* “borrowing hydrogen

Entry <sup>a</sup>	Alcohol	Ethyl ester	Compound N <sup>o</sup>	Yield (%) <sup>b</sup>
1			<b>169</b>	88
2			<b>170</b>	81
3			<b>171</b>	82
4			<b>172</b>	72
5			<b>173</b>	80 <sup>c</sup>
6			<b>174</b>	72
7			<b>175</b>	71
8			<b>176</b>	86
9			<b>177</b>	73 <sup>c</sup>
10			<b>178</b>	77 <sup>c</sup>
11			<b>179</b>	75 <sup>c</sup>
12			<b>180</b>	100 <sup>d</sup>

<sup>a</sup> Reactions carried out on 4 mmol scale. <sup>b</sup> Isolated after column chromatography, except where stated. <sup>c</sup> Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> (5 mol %) and KOH 12.5 mol % used in these examples. <sup>d</sup> The product was formed with 100% conversion of alcohol using mono-benzylmalonic ester but also contained benzyl acetate (resulting from decarboxylation of the starting material).

**Table 20.** Alkanes synthesised from alcohols and malonate half esters.

Therefore, under the reaction conditions of 2.5 mol % Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> **15**, 6.25 mol% KOH 30 mol% pyrrolidine and 20 mol% *iso*-propanol a range of alcohols were converted into the doubly homologated esters using 1.5 equivalents of mono-ethyl malonate after reflux in toluene for 24 hours (**Table 20**).

The reaction proved to be successful for a range of benzylic alcohols (**Table 20, entries 1-9**), including the *p*-fluoro, *p*-chloro- and *p*-bromo-substituted alcohols in **entries 2-4**. Electron rich benzylic alcohols (**entries 6 and 7**) and the heterocyclic 2-thienylmethanol (**entry 9**) were also successful. However the electron deficient *p*-trifluoromethyl substituted benzyl alcohol (**entry 5**) and the aliphatic alcohols were less reactive and required a higher catalyst loading to reach completion under these conditions. The lower reactivity of these alcohols parallels the expected ease of oxidations for these substrates.

The same reaction conditions were employed in using mono-benzyl malonic ester to give the benzyl ester product in entry 12. Whilst the product was still formed with 100% conversion, it was contaminated with the involatile benzyl acetate, presumably formed by decarboxylation of the starting monoester. Use of the potassium salts of mono-ethyl and mono-methyl malonate under these conditions proved unsuccessful.

Other malonate type nucleophiles were briefly investigated in these reactions. Use of cyanoacetic acid for example gave no conversion to products. Diesters of the malonates can be used in such systems,<sup>8</sup> and as an alternative to the decarboxylative alkene formation nitroalkanes can be used in a tandem alcohol oxidation/nitroaldol condensation process.<sup>30</sup> However, the scope of the reactions outlined above are limited to malonate half-esters at this time.

**4.12 Chapter summary**

- Used the ruthenium xanphos catalyst system to synthesis a range of  $\alpha,\beta$ -unsaturated ester from alcohols by using a tandem oxidation, decarboxylative condensation reaction.
- The same methodology was applied in the double homologation of alcohols to fully saturated esters after optimisation, by the “borrowing hydrogen” methodology.
- The results of this study have been published.<sup>30, 31</sup>

**4.13 References**

1. Cadierno, V.; Crochet, P.; Gimeno, J., *Synlett* **2008**, 1105.
2. Suzuki, T.; Tokunaga, M.; Wakatsuki, Y., *Tetrahedron Lett* **2002**, 43, 7531.
3. Trost, B. M.; Livingston, R. C., *J. Am. Chem. Soc* **1995**, 117, 9586.
4. Trost, B. M.; Livingston, R. C., *J. Am. Chem. Soc.* **2008**, 130, 11970.
5. Owston, N. A.; Parker, A. J.; Williams, J. M. J., *Chem. Commun.* **2008**, 624.
6. Ledger, A. E. W.; Slatford, P. A.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J., *Dalton Trans.* **2009**, 716.
7. de Vries, J. G.; Roelfes, G.; Green, R., *Tetrahedron Lett.* **1998**, 39, 8329.
8. Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J., *Tetrahedron Lett.* **2006**, 47, 6787.
9. Maiella, P. G.; Brill, T. B., *J. Phy. Chem.* **1996**, 100, 14352.
10. List, B.; Doebling, A.; Fonseca, M. T. H.; Wobser, K.; van Thienen, H.; Torres, R. R.; Galilea, P. L., *Adv. Synth. Catal.* **2005**, 347, 1558.
11. List, B.; Doebling, A.; Fonseca, M. T. H.; Job, A.; Torres, R. R., *Tetrahedron* **2006**, 62, 476.
12. Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A., *Acc. Chem. Res.* **2005**, 38, 851.
13. Ireland, R. E.; Norbeck, D. W., *J. Org. Chem.* **1985**, 50, 2198.
14. MacCoss, R. N.; Balskus, E. P.; Ley, S. V., *Tetrahedron Lett.* **2003**, 44, 7779.
15. Kinastowski, S.; Mroczyk, W., *Pol. J. Chem.* **1984**, 58, 179.
16. Hann, A. C. O.; Lapworth, A., *J. Chem. Soc.* **1904**, 85, 46.
17. Kinastowski, S.; Mroczyk, W., *Bull. Pol. Acad. Sci., Chem.* **1989**, 37, 109.
18. Niwayama, S., *J. Synth. Org. Chem. Jpn.* **2008**, 66, 983.
19. Corey, E. J., *J. Am. Chem. Soc.* **1952**, 72, 5897.
20. Corey, E. J., *J. Am. Chem. Soc.* **1953**, 75, 1163.
21. Edwards, M. G.; Williams, J. M. J., *Angew. Chem.-Int. Ed.* **2002**, 41, 4740.
22. Black, P. J.; Edwards, M. G.; Williams, J. M. J., *Eur. J. Org. Chem.* **2006**, 4367.
23. Naota, T.; Takaya, H.; Murahashi, S. I., *Chem. Rev.* **1998**, 98, 2599.
24. Sasson, Y.; Blum, J., *Tetrahedron Lett.* **1971**, 24, 2167.
25. Blum, J.; Sasson, Y.; Iflah, S., *Tetrahedron Lett.* **1972**, 11, 1015.
26. Sasson, Y.; Blum, J., *J. Org. Chem.* **1975**, 40, 1887.
27. Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C., *J. Org. Chem.* **2001**, 66, 9020.
28. Chowdhury, R. L.; Backvall, J. E., *J. Chem. Soc. Chem. Commun.* **1991**, 1063.
29. Fujita, K.; Yamaguchi, R., *Synlett* **2005**, 560.

30. Hall, M. I.; Pridmore, S. J.; Williams, J. M. J., *Adv. Synth. Catal.* **2008**, 350, 1975.
31. Pridmore, S. J.; Williams, J. M. J., *Tetrahedron Lett.* **2008**, 49, 7413.

## 5 Experimental

### 5.1 General Experimental Methods

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen or argon. In all cases, solvents were distilled or obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system or by distillation. Where stated, apparatus was oven dried or flame dried under vacuum and purged with inert gas by three cycles of removal under vacuum and replacement with inert gas where appropriate.

Screening reactions were carried out in parallel using a Radleys or Electrothermal carousel under an inert atmosphere.

TLC using polythene, aluminium or glass backed plates recoated with Macherey-Nagel Sil G/UV<sub>254nm</sub> neutral silica were used to monitor reactions where appropriate. Visualisation of these plates was by 254nm UV light and/or KMnO<sub>4</sub> dip, followed by gentle warming. TLC data quoted for specific compounds indicate the most suitable method of visualisation. Organic layers were routinely dried with anhydrous MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* using a Büchi rotary evaporator. Where necessary, further drying was facilitated by high vacuum. Flash chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron) purchased from Fisher Scientific.

NMR spectra were run in CDCl<sub>3</sub>, d<sup>8</sup>-PhMe, d<sup>6</sup>-DMSO, d<sup>6</sup>-benzene or d<sup>4</sup>-methanol on either a Bruker Avance 250 (250 MHz), Bruker Avance 300 (300 MHz) or Bruker Avance 400 (400 MHz) instrument and recorded at the following frequencies: proton (<sup>1</sup>H – 250/300/400 MHz), carbon (<sup>13</sup>C – 75.5/100.5 MHz). Chemical shifts are reported relative to the residual solvent peak where possible or alternatively to SiMe<sub>4</sub> (δ = 0.00 ppm) as internal standard. Coupling constants (*J*) are given in Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), septet (sep), unresolved multiplets (m) or broad (br). All structural assignments were achieved with comparison from analogous literature compounds where possible. Protons that possess



chemical but not magnetic equivalence (AA'BB'systems) as in the case of 1,4-disubstituted aromatics are reported as multiplets or doublets, depending on their appearance in the spectra.

Melting points were carried out on a Gallenkamp MF-370 hot stage melting point apparatus and are uncorrected.

GC was performed using a Fison Instruments 8000GC Series instrument fitted with a 30m x 0.32 mm HP-Innowax column where a detector temperature of 250 °C and injector temperature of 250 °C were routinely used. GC-MS was performed using a Hewlett-Packard 5890 Series II instrument.

IR spectra were recorded as nujol mulls or liquid films using a Nicolet NEXUS FT-IR spectrometer or a Perkin Elmer FT-IR 100 spectrometer using a Universal ATR accessory for sampling (with internal background scan). Absorption maxima ( $\nu_{\text{max}}$ ) are recorded in wavenumbers ( $\text{cm}^{-1}$ ) and classified as strong (s), medium (m), weak (w) or broad (br).

Mass spectra were recorded using electron spray ionisation (ESI) using a microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany); this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10  $\mu\text{L}$  of sample were injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10  $\mu\text{L}$  of calibrant of 5 mM sodium formate were injected after each sample.

Unless Preparative details are provided, all reagents were commercially available and purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar, Avocado, Fluka, Lancaster and Strem Chemicals. Compounds known in the literature are referenced where appropriate in the procedure/compound title.

## 5.2 Experimental procedures: Chapter 2

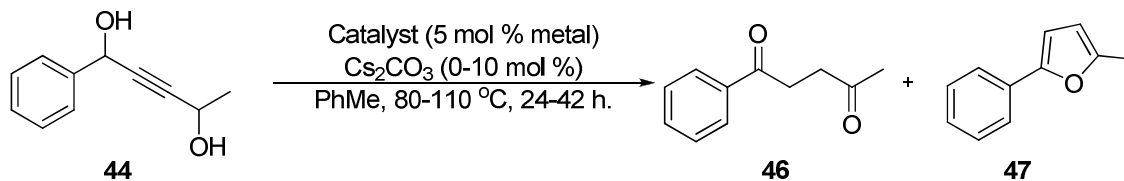
### 5.2.3 Procedure for NMR experiments of isomerisation of 3-hexyne-2,5-diol **41** using iridium catalysts.

To an oven dried argon-purged Schlenk tube containing 3-hexyn-2,5-diol (**41**, 114 mg, 1 mmol), were added either  $[\text{Ir}(\text{COD})\text{Cl}_2]_2$  (**48**, 16.7 mg, 0.025 mmol, 0.025 equiv.) or  $[\text{IrCp}^*\text{Cl}_2]_2$  (**50**, 19.9 mg 0.025 mmol, 0.025 equiv.) and caesium carbonate (32.5 mg, 0.1 mmol, 0.1 equiv.) with (1 mL) anhydrous degassed toluene. Addition of dppp (**49**, 41.2 mg, 0.1 mmol) was required for the reaction using  $[\text{Ir}(\text{COD})\text{Cl}_2]_2$  **48**. The reaction was stirred at room temperature until a homogeneous solution was attained and then a 0.5 mL aliquot was taken and placed in an argon purged Young's tap NMR tube. The toluene was removed *in vacuo* and the reactant redissolved in  $\text{d}^8$  toluene under argon. The reaction was heated for 72 hours at 80 °C.  $^1\text{H}$  NMR spectra were recorded at 24, 48 and 72 hour intervals. Conversion was determined by analysis of the peak integral ratios characteristic of 2,5-hexadione **42** and 2,5-dimethyl furan **43** in the NMR spectrum.

#### Representative procedure for attempted isomerisation of 1,4-alkyne diols.

To an oven dried, argon purged Young's tap carousel tube containing 1-phenyl-pent-2-yne-1,4-diol (**44**, 176 mg, 1mmol) and  $[\text{Ir}(\text{COD})\text{Cl}_2]_2$  (**48**, 16.7 mg, 0.025 mmol, 0.025 equiv.), caesium carbonate (32.5 mg, 0.1 mmol, 0.1 equiv.) and dppp (**49**, 41.2 mg, 0.1mmol, 0.1 equiv.) was added degassed anhydrous toluene (1 mL) and the reaction mixture heated at reflux for 42 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, filtered through a short plug of silica gel and the solvent removed *in vacuo*. Conversion was determined by analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** of the crude reaction mixture.

### 5.2.4 Catalyst screening – Isomerisation of 1-phenyl-pent-2-yne-1,4-diol **44**

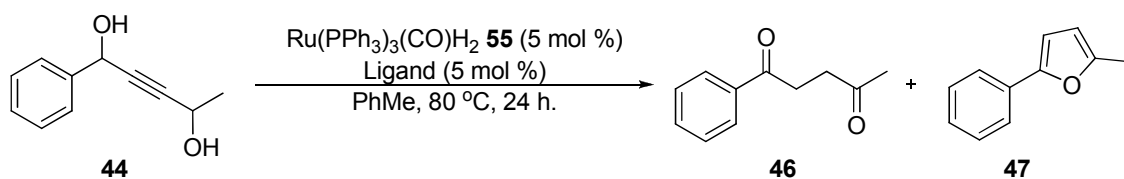


According to the general procedure using 1-phenyl-pent-2-yne-1,4-diol (**44**, 176 mg, 1 mmol) with catalysts **48-55** and caesium carbonate (equimolar with respect to chloride in the appropriate systems). Conversions as illustrated in **Table 2**, were determined by analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** of the crude reaction mixture.

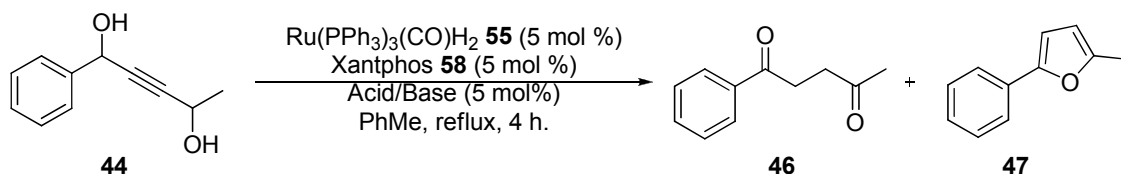
#### Ruthenium catalysed isomerisation of 1-phenyl-pent-2-yne-1,4-diol **44**

According to the general procedure using 1-phenyl-pent-2-yne-1,4-diol **44** (88 mg, 0.5 mmol) ruthenium catalysts **56-59** at 5 mol % loading with ligands **33**, **49**, **58** and **59** at 5 mol % and potassium carbonate (equimolar to chloride) as shown in **Table 3**. The reactions were heated at 80 °C for 24 hours. Conversions as illustrated in **Table 3**, were determined by analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** of the crude reaction mixture.

### 5.2.5 Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55** catalysed isomerisation of 1-phenyl-pent-2-yne-1,4-diol **44** ligand screen



To an oven-dried Young's tap carousel tube containing 1-phenyl-pent-2-yne-1,4-diol (**44**, 176 mg, 1mmol) with Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 45.8 mg, 0.05 mmol, 0.05 equiv.) and ligands **33**, **49**, **58** and **59** (0.05 mmol, 0.05 equiv.) as shown in **Table 4**, was added degassed, anhydrous toluene (1 mL). The reaction was heated at 80 °C for 24 hours. Conversion as illustrated in **Table 4**, were determined by analysis of the peak integral rations characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

**Acid/base screen for tandem isomerisation cyclisation reaction.**

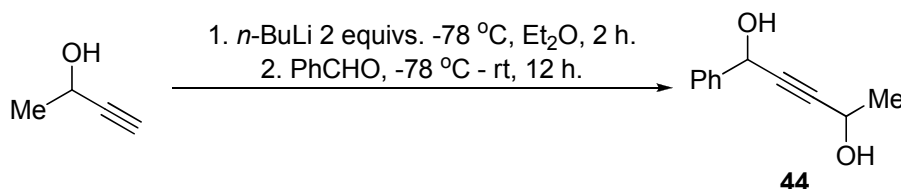
To an oven dried Young's tap carousel tube containing 1-phenyl-pent-2-yne-1,4-diol (**44**, 176 mg, 1mmol),  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  **55** (45.8 mg, 0.05 mmol, 0.05 equiv), xantphos (**58**, 28.9 mg 0.05 mmol, 0.05 equiv.) and acid or base (0.05 mmol, 0.05 equiv. **Table 5**, **entries 1-10**) was added degassed, anhydrous toluene (1 mL). The reaction mixture was heated at reflux for 4 hours. On completion the reaction was allowed to cool and toluene was removed *in vacuo* and the crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

**5.2.6 Optimisation of acid co-catalyst concentration for tandem isomerisation cyclisation reaction**

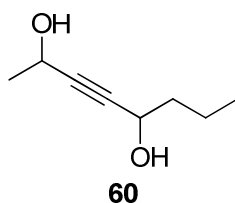
To an oven dried Young's tap carousel tube containing 1-phenyl-pent-2-yne-1,4-diol **44** (176 mg, 1mmol),  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  **55** (45.8 mg, 0.05 mmol, 0.05 equiv.), xantphos **58** (28.9 mg 0.05 mmol, 0.05 equiv.) and acetic acid (5-20 mol% as shown in **Table 6**) was added degassed anhydrous toluene (1 mL). The reaction mixture was heated at reflux for 24 hours. On completion the reaction was allowed to cool and toluene was removed *in vacuo* and the crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture

### 5.2.7 Synthesis of 1,4-alkyne diols

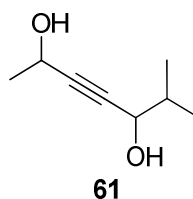
#### Representative procedure for the synthesis of 1,4-alkyne diols



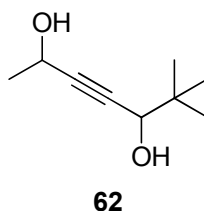
To an oven dried, argon purged 3-neck round bottom flask was added degassed anhydrous diethyl ether and 3-butyne-2-ol (1.7 mL, 30 mmol). The reaction was cooled to -78 °C and *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) was added dropwise under an argon atmosphere. The reaction was allowed to stir at -78 °C for 2 hours followed by dropwise addition of benzaldehyde (3 mL, 30 mmol). The reaction was left to warm to room temperature under argon and stirring for 12 hours. The reaction was quenched with saturated NH<sub>4</sub>Cl solution (50 mL) and extracted with ethyl acetate (2x 20 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* to afford the crude product. 1-Phenylpent-2-yne-1,4-diol **44** (Table 7, entry 1) was purified by column chromatography (6:4 Hexane/EtOAc, *R<sub>f</sub>* = 0.16) to yield a yellow oil (4.33 g, 82%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 7.45-7.25 (m, 5H), 5.40 (s, 1H), 4.51 (q, 1H, *J* = 6.6 Hz), 2.53 (br, 2H), 1.38 (d, 3H, *J* = 6.6 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 140.79, 129.03, 128.82, 127.02, 88.95, 84.16, 64.86, 58.74, 24.55; HRMS(ESI-TOF): calcd. for C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>Na<sup>+</sup>: 199.0734. Found 199.0715 (MNa<sup>+</sup>); FT-IR (neat) 3264, 2981, 2878, 2217, 1454, 1283, 1070, 695 cm<sup>-1</sup>.



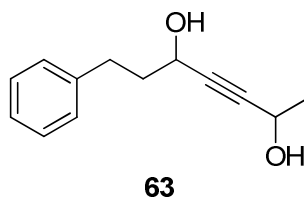
**Oct-3-yne-2,5-diol 60 (Table 7, entry 2).** According to the representative procedure using 3-butyne-2-ol (2.2 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and butyraldehyde (2.6 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f = 0.16$ ) as a yellow oil (2.64 g, 64%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 4.62$  (q, 1H,  $J = 6.6$  Hz), 4.45 (t, 1H,  $J = 6.6$  Hz), 3.98 (br, 2H), 1.71 (m 2H), 1.53 (m, 5H), 1.00 (t, 3H,  $J = 7.5$  Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 87.05, 85.43, 62.28, 58.35, 40.02, 24.53, 18.85, 14.32$ .



**6-Methylhept-3-yne-2,5-diol 61 (Table 7, entry 3).** According to the representative procedure using 3-butyne-2-ol (2.2 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 2-methylpropanal (2.7 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f = 0.15$ ) as a yellow oil (2.68 g, 63%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 4.55$  (q, 1H,  $J = 6.6$  Hz), 4.15 (m, 1H), 3.74 (br, 2H), 1.82 (p, 1H,  $J = 6.6$  Hz), 1.42 (d, 3H,  $J = 6.6$  Hz), 0.95 (t, 6H,  $J = 6.6$  Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 87.83, 84.02, 83.99, 68.02, 67.80, 58.42, 24.57, 24.57, 18.56, 18.5$ .

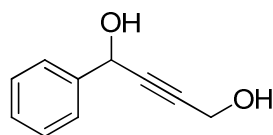


**6,6-Dimethylhept-3-yne-2,5-diol 62** (Table 7, entry 4). According to the representative procedure using 3-butyne-2-ol (2.2 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and trimethylacetaldehyde (3.25 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a white solid (3.65 g, 78%). M.P. = 78-80 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 4.50 (q, 1H,  $J$  = 6.6 Hz), 3.97 (s, 1H), 2.76 (s, 1H), 2.09 (s, 1H), 1.39 (d, 3H,  $J$  = 6.6 Hz), 0.92 (s, 9H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 87.24, 83.27, 70.80, 57.85, 35.30, 24.80, 23.90; HRMS(ESI-TOF): calcd. for  $\text{C}_9\text{H}_{16}\text{O}_2\text{Na}^+$ : 179.1047. Found 179.1034 ( $\text{MNa}^+$ ); FT-IR (neat) 3287, 2968, 2954, 2869, 2181, 1466, 1145, 1010  $\text{cm}^{-1}$ .

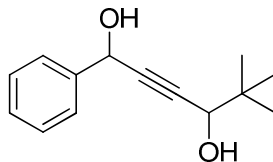


**7-Phenylhept-3-yne-2,5-diol 63** (Table 7, entry 5). According to the representative procedure using 3-butyne-2-ol (2.2 mL, 30 mmol) with *n*-butyllithium 10M (6 mL, 60 mmol) and 3-phenylpropanal (3.95 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a yellow oil (6.76 g, 51%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.18-7.0 (m, 5H), 4.41 (q, 1H,  $J$  = 6.6 Hz), 4.26 (t, 1H,  $J$  = 6.6 Hz), 2.65 (t, 2H,  $J$  = 7.8 Hz), 1.88 (t, 2H,  $J$  = 7.8 Hz), 1.31 (d, 3H,  $J$  = 6.6 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 141.78, 128.89, 128.80, 126.34, 87.48, 85.10, 61.73, 58.35, 39.58, 31.88, 24.68; HRMS(ESI-TOF): calcd. for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}^+$ : 227.1047. Found 227.1038 ( $\text{MNa}^+$ ); FT-IR (neat) 3331, 3027, 2981, 2929, 2162, 1942, 1603, 1453, 1030, 747, 697  $\text{cm}^{-1}$ .

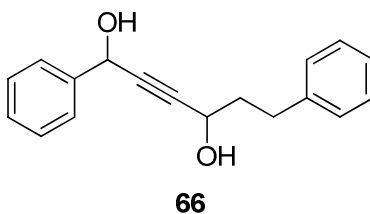


**64**

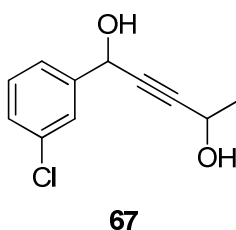
**1-Phenylbut-2-yne-1,4-diol 64** (Table 7, entry 6). According to the representative procedure using 2-propyn-1-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and benzaldehyde (3.0 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a white solid. (5.47 g, 52%) M.P. = 74-77 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.47-7.29 (m, 5H), 5.44 (s, 1H), 4.29 (s, 2H), 2.18 (br, 1H), 1.61 (br, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 140.7, 129.10, 126.97, 85.93, 85.29, 65.06, 51.61; HRMS(ESI-TOF): calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_2\text{Na}^+$ : 185.0578. Found 185.0573 ( $\text{MNa}^+$ ); FT-IR (neat) 3235, 3063, 3032, 2930, 2870, 1991, 1707, 1598, 1493, 1451, 1020, 1001  $\text{cm}^{-1}$ ; Anal. Calcd for:  $\text{C}_{10}\text{H}_{10}\text{O}_2$ : C 74.06; H, 6.21. Found C, 73.7; H, 6.32.

**65**

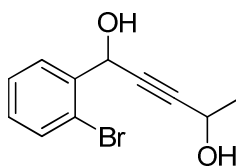
**5,5-Dimethyl-1-phenylhex-2-yne-1,4-diol 65** (Table 7, entry 7). According to the representative procedure using 1-phenyl-2-propyn-1-ol (3.6 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) trimethylacetaldehyde (3.25 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.14) as a yellow oil (4.80 g, 74%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.66-7.32 (m, 5H), 5.53 (s, 1H), 4.12 (s, 1H), 1.01 (s, 9H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 129.95, 129.05, 128.84, 126.99, 71.84, 65.08, 25.77; HRMS(ESI-TOF): calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}^+$ : 241.1204. Found 241.1202 ( $\text{MNa}^+$ ); FT-IR (neat) 3410, 3066, 2966, 2908, 2871, 2225, 1702, 1598, 1450, 1262, 1008, 697  $\text{cm}^{-1}$ .



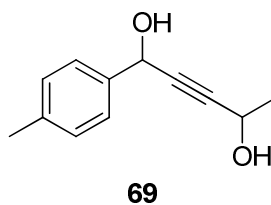
**1,6-Diphenylhex-2-yne-1,4-diol 66 (Table 7, entry 8).** According to the representative procedure using 1-phenyl-2-propyn-1-ol (3.6 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) 3-phenylpropanal (3.95 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.12) as a yellow oil (6.06 g, 76%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.43-7.06 (m, 10H), 5.37 (s, 1H), 4.31 (t, 1H,  $J$  = 6.6 Hz), 3.23 (br, 1H), 2.90 (br, 1H), 2.66 (t, 2H,  $J$  = 7.8 Hz), 1.92 (m, 2H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 141.59, 140.83, 129.04, 128.92, 128.86, 128.82, 127.06, 127.05, 126.42, 87.89, 85.44, 64.81, 62.08, 39.43, 31.81, 21.47.



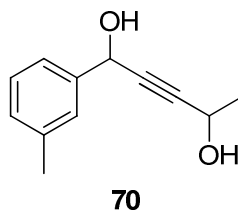
**1-(3-Chlorophenyl)pent-2-yne-1,4-diol 67 (Table 7, entry 9).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 3-chlorobenzaldehyde (3.4 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.14) as a yellow oil (7.47g, 57%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.50 (s, 1H), 7.37-7.25 (m, 3H), 5.42 (s, 1H), 4.59, (q, 1H,  $J$  = 6.6 Hz), 3.53 (br, 1H), 3.11 (br 1H), 1.45 (d, 3H,  $J$  = 6.6 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 142.68, 134.82, 130.27, 128.86, 127.17, 125.14, 89.23, 83.62, 64.03, 58.67, 24.42; HRMS(ESI-TOF): calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}^+$ : 241.1202. Found 241.1204 ( $\text{MNa}^+$ ); FT-IR (neat) 3275, 2982, 2932, 2217, 1952, 1596, 1470, 1196, 1073, 692  $\text{cm}^{-1}$ .

**68**

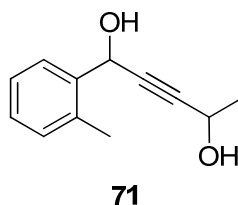
**1-(2-Bromophenyl)pent-2-yne-1,4-diol 68** (Table 7, entry 10). According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 2-bromobenzaldehyde (3.5 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.14) as a white solid (12.56 g, 76%). M.P. = 81-86 °C;  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 7.67 (dt, 1H,  $^3J$  = 7.7 Hz,  $^4J$  = 1.5 Hz), 7.48 (dd, 1H,  $^3J$  = 7.7 Hz,  $^4J$  = 1.5 Hz), 7.28 (dt, 1H,  $^3J$  = 7.7 Hz,  $^4J$  = 1.5 Hz), 7.12 (dt, 1H,  $^3J$  = 7.7 Hz,  $^4J$  = 1.5 Hz), 5.74 (d, 1H,  $J$  = 4.0 Hz), 4.52 (m, 1H), 2.84 (t, 1H,  $J$  = 6.0 Hz), 2.27 (t, 1H,  $J$  = 6.0 Hz), 1.39 (d, 3H,  $J$  = 6.0 Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 139.69, 133.41, 130.36, 128.92, 128.30, 123.07, 89.07, 83.12, 64.43, 58.79, 24.47; HRMS(ESI-TOF): calcd. for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{BrNa}^+$ : 276.9840. Found 276.9825 ( $\text{MNa}^+$ ); FT-IR (neat) 3254, 2978, 2872, 2183, 1568, 1468, 1431, 1147, 1079, 994, 751  $\text{cm}^{-1}$ ; Anal. Calcd for:  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Br}$ : C 51.79; H, 4.35. Found C, 52.2; H, 4.39.



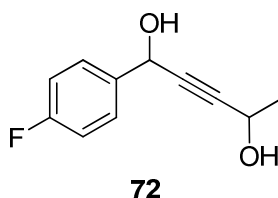
**1-*p*-Tolylpent-2-yne-1,4-diol 69** (Table 7, entry 11). According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and *p*-tolualdehyde (3.5 mL, 30 mmol) The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a yellow oil (3.36 g, 59%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 7.25 (dd, 2H,  $^3J$  = 8.0 Hz,  $^4J$  = 1.8 Hz), 7.03 (d, 2H,  $J$  = 8.0 Hz), 5.29 (s, 1H), 4.44 (q, 1H,  $J$  = 6.6 Hz), 3.88 (br, 1H), 3.68 (br 1H), 2.23 (s 3H), 1.31 (d, 3H,  $J$  = 6.6 Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 140.83, 138.61, 138.42, 129.60, 127.09, 88.75, 84.33, 64.55, 58.52, 24.41, 21.80; FT-IR (neat) 3363, 2983, 2926, 2243, 1735, 1509, 1442, 1077, 903, 733, 651  $\text{cm}^{-1}$ .



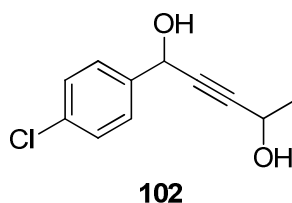
**1-*m*-Tolylpent-2-yne-1,4-diol 70** (Table 7, entry 12). According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and *m*-tolualdehyde (3.5 mL, 30 mmol) The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a yellow oil (3.36 g, 59%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 7.17-6.98 (m, 4H), 5.27 (s, 1H), 4.41 (m, 2H), 4.12 (br 1H), 3.22 (s, 3H), 1.29 (d, 3H,  $J$  = 6.6 Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 140.83, 138.59, 129.20, 128.87, 127.80, 124.18, 88.71, 84.30, 64.52, 58.47, 24.37, 21.80; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}^+$ : 213.0891. Found 213.0881 ( $\text{MNa}^+$ ); FT-IR (neat) 3594, 3363, 2983, 2921, 2253, 1791, 1730, 1606, 1452, 1375, 1160, 1139, 1077, 913, 723, 649  $\text{cm}^{-1}$ .



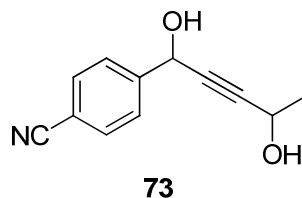
**1-*o*-Tolylpent-2-yne-1,4-diol 71 (Table 7, entry 13).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and *o*-tolualdehyde (3.5 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.16) as a white solid (7.16 g, 58%). M.P. = 73-77 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.62 (m, 1H), 7.27-7.16 (m, 3H), 5.63 (s, 1H), 4.59 (q, 1H,  $J$  = 6.6 Hz), 2.43 (s, 3H), 1.46 (d, 3H,  $J$  = 6.6 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 138.55, 136.25, 131.16, 128.85, 126.84, 126.62, 88.77, 83.92, 62.67, 58.77, 24.56, 19.33. HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}^+$ : 213.0891. Found 213.0890 ( $\text{MNa}^+$ ); FT-IR (neat) 3358, 2983, 2931, 2248, 1735, 1488, 1149, 1077, 908, 733, 651  $\text{cm}^{-1}$ ; Anal. Calcd for:  $\text{C}_{12}\text{H}_{14}\text{O}_2$ : C 75.76; H, 7.42. Found C, 75.76.2; H, 7.42.



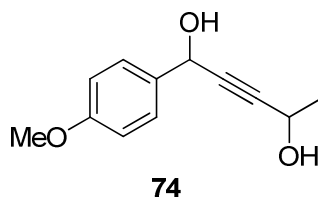
**1-(4-Fluorophenyl)pent-2-yne-1,4-diol 72 (Table 7, entry 14).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 4-fluorobenzaldehyde (3.2 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a yellow oil (6.05 g, 48%).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.48 (m, 2H), 7.05 (m, 2H), 5.44 (s, 1H), 4.60 (q, 1H,  $J$  = 6.7 Hz), 3.80 (br, 1H), 3.43 (br, 1H), 1.45 (d, 3H,  $J$  = 6.7 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 161.71, 136.68, 128.82, 115.99, 115.71, 89.09, 83.99, 64.11, 58.70, 24.49; HRMS(ESI-TOF): calcd. for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{FNa}^+$ : 217.0640. Found 217.0616 ( $\text{MNa}^+$ ); FT-IR (neat) 3277, 2987, 2880, 2224, 1647, 1598, 1506, 1222, 1151, 1077, 837  $\text{cm}^{-1}$ .



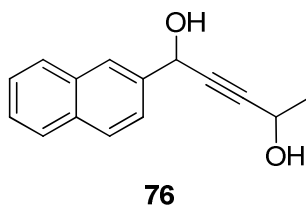
**1-(4-Chlorophenyl)pent-2-yne-1,4-diol 102.** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 4-chlorobenzaldehyde (4.2 g, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.15) as a yellow oil (4.30 g, 69%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 7.44-7.19 (m, 4H), 5.35 (s, 1H), 4.87 (br, 1H), 4.50 (q, 1H,  $J$  = 6.6 Hz), 4.35 (br, 1H), 1.37 (d, 3H,  $J$  = 6.6 Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 142.91, 134.63, 130.18, 129.88, 128.64, 127.14, 125.21, 89.00, 83.56, 63.72, 58.40, 24.33. HRMS(ESI-TOF): calcd. for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{ClNa}^+$ : 233.0316. Found 233.0340 ( $\text{MNa}^+$ ); FT-IR (neat) 3325, 2984, 2222, 1643, 1586, 1260, 1089, 1009, 746  $\text{cm}^{-1}$ .



**4-(1,4-Dihydroxypent-2-ynyl)benzonitrile 73 (Table 7, entry 15).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 4-formylbenzonitrile (3.9 g, 30 mmol). The title compound was synthesised and purified by column chromatography (1:1 Hexane/EtOAc,  $R_f$  = 0.23) as a yellow solid (7.18 g, 55%); M.P. = 86-90 °C;  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 7.58 (m, 4H), 5.48 (s, 1H), 4.53 (q, 1H,  $J$  = 6.6 Hz), 2.88 (br, 1H), 2.27 (br, 1H), 1.40 (d, 3H,  $J$  = 6.6 Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}}$  = 145.76, 132.81, 127.57, 118.96, 112.47, 89.75, 83.11, 63.99, 58.71, 53.82, 24.53; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{11}\text{NO}_2\text{Na}^+$ : 224.0687. Found 224.0679 ( $\text{MNa}^+$ ); FT-IR (neat) 3277, 3164, 2978, 2227, 1708, 1609, 1294, 1270, 1074, 1011, 989, 822  $\text{cm}^{-1}$ .

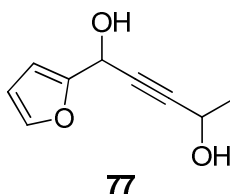


**1-(4-Methoxyphenyl)pent-2-yne-1,4-diol 74** (Table 7, entry 16). According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and anisaldehyde (3.6 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (1:1 Hexane/EtOAc,  $R_f = 0.24$ ) as a yellow oil (8.57 g, 64%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 7.45$  (d, 2H,  $J = 9.0$  Hz), 6.89 (d, 2H,  $J = 9.0$  Hz), 5.43 (s, 1H), 4.60 (q, 1H,  $J = 6.6$  Hz), 3.81, (s, 3H), 2.55 (br, 1H), 2.31 (br, 1H), 1.47 (d, 3H,  $J = 6.6$  Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 160.11, 133.15, 128.45, 114.38, 88.79, 84.31, 64.50, 58.77, 55.73, 24.60$ ; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}^+$ : 229.0840. Found 229.0821 ( $\text{MNa}^+$ ); FT-IR (neat) 3359, 2982, 2839, 1734, 1710, 1611, 1510, 1243, 1173, 1029, 832  $\text{cm}^{-1}$ .

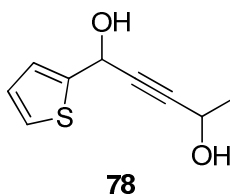


**1-(Naphthalen-2-yl)pent-2-yne-1,4-diol 76** (Table 7, entry 18). According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 2-naphthaldehyde (4.68 g, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f = 0.15$ ) as a white solid (10.30 g, 70%). M.P. 99-104 °C;  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 8.20$  (d, 1H,  $J = 8.1$  Hz), 7.83-7.74 (m, 3H), 7.52-7.38 (m, 3H), 6.08 (d, 1H,  $J = 6$  Hz), 4.56 (p, 1H,  $J = 6.6$  Hz), 2.32 (d, 1H,  $J = 6.6$  Hz), 1.86 (d, 1H,  $J = 6.6$  Hz), 1.42 (d, 3H,  $J = 6.6$  Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 135.79$ , 134.42, 130.88, 129.84, 129.17, 126.86, 126.33, 125.61, 124.96, 124.23, 89.60, 83.90, 63.24, 58.89, 24.60; HRMS(ESI-TOF): calcd. for  $\text{C}_{15}\text{H}_{14}\text{O}_2\text{Na}^+$ : 249.0891. Found 249.0884 ( $\text{MNa}^+$ ); FT-IR (neat) 3235, 2971, 2181, 1509, 1477, 1147, 1075, 988, 782  $\text{cm}^{-1}$ ; Anal. Calcd for:  $\text{C}_{15}\text{H}_{14}\text{O}_2$ : C 79.62; H, 6.24. Found C, 79.50.2; H, 6.32.



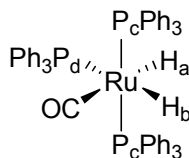


**1-(Furan-2-yl)pent-2-yne-1,4-diol 77 (Table 7, entry 19).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 2-furaldehyde (2.5 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.16) as a brown solid (4.10 g, 38%); M.P. 67-69 °C; **NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.42 (dd, 1H,  $J$  = 1.8 Hz, 0.9 Hz), 6.43 (d, 1H,  $J$  = 3.3 Hz), 6.36 (dd, 1H,  $J$  = 3.2 Hz, 1.8 Hz), 5.50 (s, 1H), 4.62 (q, 1H,  $J$  = 6.6 Hz), 2.64 (br, 1H), 2.21 (br, 1H), 1.49 (d, 3H,  $J$  = 6.6 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 153.08, 143.44, 110.82, 108.22, 88.17, 81.67, 58.72, 58.49, 24.46; HRMS(ESI-TOF): calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>Na<sup>+</sup>: 189.0527. Found 189.0510 (MNa<sup>+</sup>); 3269, 2980, 2217, 1629, 1374, 1323, 1271, 1230, 1148, 1078, 1010, 993, 740 cm<sup>-1</sup>; Anal. Calcd for: C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>: C 65.05; H, 6.07. Found C, 64.60; H, 5.98.



**1-(thiophen-2-yl)pent-2-yne-1,4-diol 78 (Table 7, entry 20).** According to the representative procedure using 3-butyne-2-ol (1.7 mL, 30 mmol) with *n*-butyllithium (10 M in hexanes 6 mL, 60 mmol) and 2-thiophene carboxaldehyde (2.2 mL, 30 mmol). The title compound was synthesised and purified by column chromatography (6:4 Hexane/EtOAc,  $R_f$  = 0.16) as a brown solid (2.6 g, 22%); M.P. 77-81 °C; **NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.40 (m, 1H), 7.31 (dd, 1H  $J$  = 5.0Hz, 3.0Hz), 7.19 (dd, 1H,  $J$  = 5.0 Hz, 1.3 Hz), 5.54 (s, 1H), 4.62 (q, 1H,  $J$  = 6.6 Hz), 1.50 (d, 3H,  $J$  = 6.6 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 142.16, 126.88, 123.12, 88.10, 84.02, 60.65, 58.59, 24.46; HRMS(ESI-TOF): calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>SNa<sup>+</sup>: 205.0299. Found 205.0285 (MNa<sup>+</sup>); FT-IR (neat) 3270, 2979, 2931, 2162, 1630, 1373, 1271, 1147, 1075, 1008, 993, 739 cm<sup>-1</sup>; Anal. Calcd for: C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>S: C 59.32; H, 5.53. Found C, 60.4; H, 5.29.

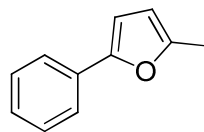
**Preparation of carbonyl(dihydro)tris(triphenylphosphine)ruthenium(II):  
Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> **55**<sup>1</sup>**

**55**

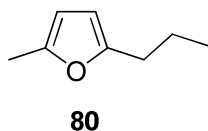
To an argon-purged, 3-necked round bottomed flask charged with triphenylphosphine (6.28 g, 23.9 mmol) was added degassed anhydrous methanol (200 mL). The mixture was heated at reflux for 10 minutes, forming a solution. In quick succession, ruthenium trichloride hydrate (1.04 g, 4.0 mmol) in methanol (40 mL), aqueous formaldehyde (37% w/w) (40 mL) and potassium hydroxide (1.20 g, 21.4 mmol) in methanol (40 mL) were added. The resulting solution was heated for 30 minutes at reflux and then cooled in an ice bath with stirring for a further 30 minutes. The grey precipitate was collected by vacuum filtration and washed with absolute ethanol (50 mL), water (50 mL), absolute ethanol (50 mL) and finally hexane (50 mL). The crude product was dissolved in toluene and filtered through a column of neutral alumina and washed through thoroughly with toluene. The toluene solution was concentrated *in vacuo* to approximately 20 mL and layered with anhydrous methanol producing a precipitated which was collected by vacuum filtration yielding the title compound **55** as a white solid (2.50g, 68%). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>): δ<sub>ppm</sub> = -6.53 (ddt, 1H Ru-H<sub>a</sub>, J<sub>Pc-Ha</sub> = 30.5 Hz, J = J<sub>Pd-Ha</sub> = 15.3 Hz, J<sub>Ha-Hb</sub> = 6.1 Hz), -8.29 (ddt, 1H, Ru-H<sub>b</sub>, J<sub>Pd-Hb</sub> = 74.5 Hz, J<sub>Pc-Hb</sub> = 28.1 Hz, J<sub>Ha-Hb</sub> = 6.1 Hz). <sup>31</sup>P {<sup>1</sup>H}: δ<sub>ppm</sub> = 58.2 (d, J<sub>Pc-Pd</sub> = 16.8 Hz), 46.1 (t, J<sub>Pd-Pc</sub> = 16.8 Hz). IR (nujol mull, cm<sup>-1</sup>): 1960.

### 5.2.8 Synthesis of 2,5-disubstituted furans using a isomerisation cyclocondensation tandem reaction.

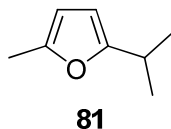
#### Representative procedure

**79**

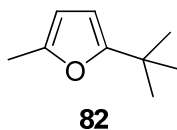
**2-Methyl-5-phenylfuran 79<sup>2</sup>** (Table 8, entry 1). To an oven dried, argon purged Young's tap carousel tube charged with 1-phenylpent-2-yne-1,4-diol (**44**, 352 mg, 2 mmol), Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 18.3 mg, 0.01 mmol, 0.01 equiv.), xantphos (**58**, 11.5 mg, 0.01 mmol, 0.01 equiv) and acid co-catalyst (acetic, propionic or benzoic 5.7  $\mu$ L, 7.4  $\mu$ L, 12.2 mg respectively, 0.05 mmol, 0.05 equiv.), degassed anhydrous toluene (1 mL) was added and the reaction heated at reflux for 24 hours. The solvent was removed *in vacuo* and the crude reaction mixture analysed by <sup>1</sup>H NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46** and 1-phenyl-5-methyl furan **47** in the <sup>1</sup>H NMR spectrum of the crude reaction mixture. The crude reaction mixture was purified by column chromatography (hexane, R<sub>f</sub> = 0.47) and the title compound was afforded as a clear oil (256.5 mg, 80%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.55 (dd, 2H, *J* = 7 Hz, 1.3 Hz), 7.27 (t, 2H, *J* = 7.3 Hz), 7.12 (m, 1H), 6.44 (d, 1H, *J* = 3.2 Hz), 5.96 (m, 1H), 2.28 (s, 3H). **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 152.70, 152.34, 131.60, 128.98, 128.63, 127.13, 123.70, 108.07, 106.24, 14.10; HRMS(ESI-TOF): calcd. for C<sub>11</sub>H<sub>10</sub>OH<sup>+</sup>: 159.0804. Found 159.0802 (MH<sup>+</sup>); FT-IR (neat) 3077, 3025, 2951, 2918, 1883, 1683, 1595, 1545, 1479, 1444, 1203, 1021, 791, 760, 692 cm<sup>-1</sup>.



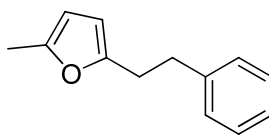
**2-Methyl-5-propylfuran 80** (Table 8, entry 2). According to the general procedure using oct-3-yne-2,5-diol (**60**, 284 mg, 2 mmol) 2-methyl-5-propylfuran **80** was synthesised. Analysis of the crude reaction mixture by gas chromatography showed 95% conversion with 73% furan (RT 7.02 min @ 170 °C, 30m x 0.32 mm HP-Innowax column. FID).



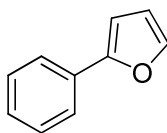
**2-Isopropyl-5-methylfuran 81** (Table 8, entry 3). According to the general procedure using 6-methylhept-3-yne-2,5-diol (**61**, 284 mg, 2 mmol) 2-isopropyl-5-methylfuran **81** was synthesised. Analysis of the crude reaction mixture by gas chromatography showed 94% conversion with 79% furan (RT 9.56 min @ 170 °C, 30m x 0.32 mm HP-Innowax column. FID).



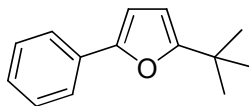
**2-tert-Butyl-5-methylfuran 82** (Table 8 entry 4). According to the general procedure using 6,6-dimethylhept-3-yne-2,5-diol (**62**, 312 mg, 2 mmol) 2-tert-butyl-5-methylfuran **82** was synthesised. Analysis of the crude reaction mixture by gas chromatography showed 100% conversion with 93% furan (RT 5.75 min @ 170 °C, 30m x 0.32 mm HP-Innowax column. FID).

**83**

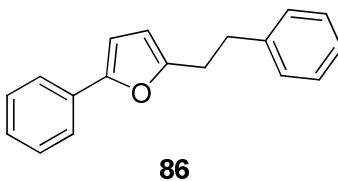
**2-Methyl-5-phenethylfuran 83** (Table 8, entry 5). According to the general procedure using 7-Phenylhept-3-yne-2,5-diol (**63**, 408 mg, 2 mmol) 2-methyl-5-phenethylfuran **83** was synthesised. Analysis of the crude reaction mixture by gas chromatography showed 100% conversion with 91% furan (RT 7.91 min @ 170 °C, 30m x 0.32 mm HP-Innowax column. FID).

**84**

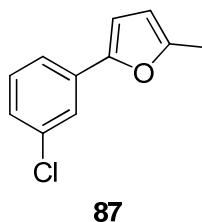
**2-Phenylfuran 84** (Table 8, entry 6) According to the general procedure using 1-phenylbut-2-yne-1,4-diol (**64**, 324 mg, 2 mmol) 2-Phenylfuran **84** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 96% furan.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.74 (m, 1H), 7.16-7.05 (m, 5H), 6.51 (dd, 1H,  $J$  = 3.3 Hz, 0.7 Hz), 6.26 (dd, 1H,  $J$  = 3.3 Hz, 1.8 Hz).

**85**

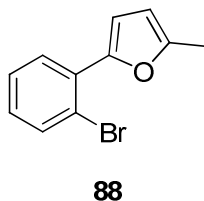
**2-tert-Butyl-5-phenylfuran 85** (Table 8, entry 7). According to the general procedure using 5,5-dimethyl-1-phenylhex-2-yne-1,4-diol (**65**, 436 mg, 2 mmol) 2-tert-butyl-5-phenylfuran **85** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 80% furan.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.30-7.08 (m 5H), 6.45 (d, 1H,  $J$  = 3.2 Hz), 5.97 (d, 1H,  $J$  = 3.2 Hz), 1.26 (s, 9H).



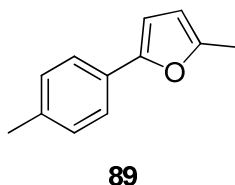
**2-Phenethyl-5-phenylfuran 86 (Table 8, entry 8).** According to the general procedure using 1,6-diphenylhex-2-yne-1,4-diol (**66**, 532 mg, 2 mmol) 2-phenethyl-5-phenylfuran **86** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 76% furan.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.28-7.12 (m, 10H), 6.45 (d, 1H,  $J$  = 3.2 Hz), 5.97 (d, 1H,  $J$  = 3.2 Hz), 2.84-2.74 (m, 4H).



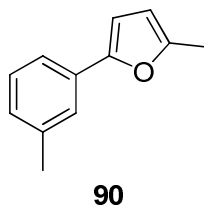
**2-(3-Chlorophenyl)-5-methylfuran 87 (Table 8, entry 9).** According to the general procedure using 1-(3-Chlorophenyl)pent-2-yne-1,4-diol (**67**, 421 mg, 2 mmol) 2-(3-chlorophenyl)-5-methylfuran **87** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 77% furan. The crude reaction mixture was purified by column chromatography (hexane,  $R_f$  = 0.48) and the title compound was afforded as a clear oil (226 mg, 58%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.62 (m, 1H), 7.50 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 6.57 (d, 1H,  $J$  = 3.2 Hz), 6.07 (m, 1H), 2.38 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 153.03, 151.24, 135.04, 133.22, 130.26, 126.98, 123.67, 121.70, 108.31, 107.43, 14.09.; HRMS(ESI-TOF): calcd. for  $\text{C}_{10}\text{H}_9\text{ClOH}^+$ : 181.0415. Found 181.0404 ( $\text{MH}^+$ ).



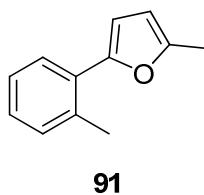
**2-(2-Bromophenyl)-5-methylfuran 88 (Table 8, entry 10).** According to the general procedure using 1-(2-Bromophenyl)pent-2-yne-1,4-diol (**68**, 510 mg, 2 mmol) 2-(2-bromophenyl)-5-methylfuran **88** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 91% furan. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.46$ ) and the title compound was afforded as a clear oil (328 mg, 77%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 7.81$  (dd, 1H,  $J = 7.9$  Hz, 1.7 Hz), 7.64 (m, 1H,  $J = 7.9$  Hz, 1.2 Hz), 7.35 (m, 1H), 7.09 (m, 2H), 6.14 (m, 1H), 2.40 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 152.59$ , 149.97, 134.49, 131.83, 128.68, 128.19, 127.71, 119.54, 112.54, 108.07, 14.07. HRMS(ESI-TOF): calcd. for  $\text{C}_{11}\text{H}_9\text{OBrH}^+$ : 236.9910. Found 236.0986 ( $\text{MH}^+$ ).



**2-Methyl-5-*p*-tolylfuran 89 (Table 8, entry 11).** According to the general procedure using 1-*p*-tolylpent-2-yne-1,4-diol (**69**, 380 mg, 2 mmol) 2-methyl-5-*p*-tolylfuran **89** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 81% furan. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.45$ ) and the title compound was afforded as a clear oil (278 mg, 79%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 7.39$  (d, 2H,  $J = 8.2$  Hz), 7.01 (d, 2H,  $J = 8.2$  Hz), 6.33 (d, 1H,  $J = 3.2$  Hz), 5.89 (d, 1H,  $J = 3.2$  Hz) 2.21 (s, 3H), 2.20 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 153.04$ , 151.94, 131.64, 129.40, 128.80, 124.13, 108.80, 105.59, 21.95, 14.14.

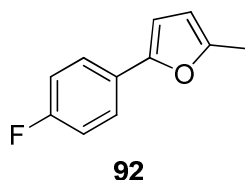


**2-Methyl-5-*m*-tolylfuran 90** (Table 8, entry 12). According to the general procedure using 1-*m*-tolylpent-2-yne-1,4-diol (**70**, 380 mg, 2 mmol) 2-methyl-5-*m*-tolylfuran **90** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 81% furan. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.45$ ) and the title compound was afforded as a clear oil (276 mg, 78%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 7.59$  (m, 2H), 7.36 (t, 1H,  $J = 7.6$  Hz), 7.15 (d, 1H,  $J = 7.6$  Hz), 6.63 (d, 1H,  $J = 3.2$  Hz), 6.16 (m, 1H), 2.49 (s, 3H), 2.48 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 152.99, 152.25, 138.64, 131.66, 129.03, 128.09, 124.45, 121.04, 108.19, 106.27, 29.62, 21.96, 14.16$ .

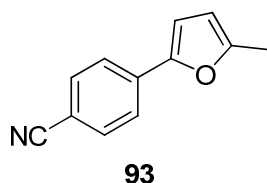


**2-Methyl-5-*o*-tolylfuran 91** (Table 8, entry 13). According to the general procedure using 1-*o*-tolylpent-2-yne-1,4-diol (**71**, 380 mg, 2 mmol) 2-methyl-5-*o*-tolylfuran **91** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 77% furan. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.32$ ) and the title compound was afforded as a clear oil (237 mg, 67%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 7.85$  (d, 1H,  $J = 8.0$  Hz), 7.40-7.26 (m, 3H), 6.55 (d, 1H, 3.2 Hz), 6.21 (m, 1H), 2.62 (s, 3H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 152.31, 151.91, 134.54, 131.62, 131.00, 128.11, 127.73, 127.06, 110.10, 108.00, 22.48, 14.13$ ; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{12}\text{OH}^+$ : 173.0894. Found 173.0923 ( $\text{MH}^+$ ).

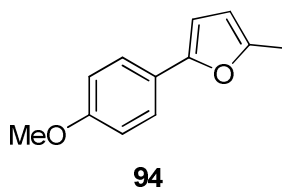




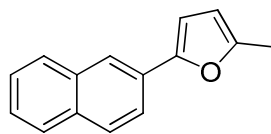
**2-(4-Fluorophenyl)-5-methylfuran 92** (Table 8, entry 14). According to the general procedure using 1-(4-Fluorophenyl)pent-2-yne-1,4-diol (**72**, 388 mg, 2 mmol) 2-(4-fluorophenyl)-5-methylfuran **92** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 83% furan  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.50 (m, 2H), 6.90 (m, 2H), 6.37 (d, 1H,  $J$  = 3.2 Hz), 5.94 (s, 1H), 2.14 (s, 3H).



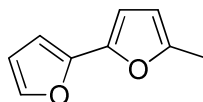
**4-(5-Methylfuran-2-yl)benzonitrile 93**<sup>3</sup> (Table 8, entry 15). According to the general procedure using 4-(1,4-Dihydroxypent-2-ynyl)benzonitrile (**73**, 402 mg, 2 mmol) 4-(5-methylfuran-2-yl)benzonitrile **93** was synthesised. The crude reaction mixture was purified by column chromatography (5:1 Petroleum ether 40-60 °C/Diethyl ether  $R_f$  = 0.51) and the title compound was afforded as a white solid (230.9 mg, 63%). M.P. = 112-115 °C (Lit M.P. = 113-115 °C).<sup>3</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.61 (d, 2H,  $J$  = 8.6 Hz), 7.55 (d, 2H,  $J$  = 8.6 Hz), 6.63 (d, 1H,  $J$  = 3.3 Hz), 6.05 (m, 1H), 2.32 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 154.40, 150.73, 135.29, 132.92, 123.74, 119.53, 109.92, 109.69, 108.89, 14.17; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_9\text{OH}^+$ : 184.0762. Found 184.0754 ( $\text{MH}^+$ ), calcd. for  $\text{C}_{12}\text{H}_9\text{ONa}^+$ : 206.0581. Found 206.0569 ( $\text{MNa}^+$ ); FT-IR (neat) 3125, 2981, 2225, 1611, 1541, 1415, 1023, 831  $\text{cm}^{-1}$ .



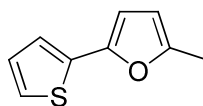
**2-(4-Methoxyphenyl)-5-methylfuran 94** (Table 8, entry 16). According to the general procedure using 1-(4-Methoxyphenyl)pent-2-yne-1,4-diol (**74**, 412 mg, 2 mmol) 2-(4-methoxyphenyl)-5-methylfuran **94** was synthesised. The crude reaction mixture was purified by column chromatography (5:1 Petroleum ether 40-60 °C/Diethyl ether  $R_f$  = 0.77) and the title compound was afforded as a yellow solid (241.7 mg, 63%). M.P. = 37-41 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.47 (d, 2H,  $J$  = 8.9 Hz), 6.81 (d, 2H,  $J$  = 8.9 Hz), 6.31 (d, 2H,  $J$  = 3.2 Hz), 5.94 (m, 1H), 3.74 (s, 3H), 2.27 (s, 3H);  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 158.99, 152.70, 151.59, 129.45, 128.64, 125.12, 114.44, 107.89, 104.60, 55.70, 14.11; HRMS(ESI-TOF): calcd. for  $\text{C}_{12}\text{H}_{12}\text{O}_2\text{H}^+$ : 189.0910. Found 189.0923 ( $\text{MH}^+$ ); FT-IR (neat) 3105, 3000, 2981, 2838, 1579, 1614, 1497, 1019, 831, 784  $\text{cm}^{-1}$

**96**

**2-Methyl-5-(naphthalen-2-yl)furan 96<sup>4</sup>** (Table 8, entry 18). According to the general procedure using 1-(Naphthalen-2-yl)pent-2-yne-1,4-diol (**76**, 452 mg, 2 mmol) 2-methyl-5-(naphthalen-2-yl)furan **96** was synthesised. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.34$ ) and the title compound was afforded as a clear oil (291.1 mg, 70%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 8.45$  (m, 1H), 7.89 (m, 1H), 7.81 (d, 1H,  $J = 8.2\text{ Hz}$ ), 7.73 (dd, 1H,  $J = 7.3\text{ Hz}$ ,  $1.2\text{ Hz}$ ), 7.52 (m, 3H), 6.62 (d, 1H,  $J = 3.1\text{ Hz}$ ), 6.19 (m, 1H), 2.46 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}} = 152.66$ , 152.04, 134.41, 130.65, 129.30, 128.87, 128.42, 126.77, 126.20, 126.03, 126.01, 125.74, 110.58, 107.87, 14.19; HRMS(ESI-TOF): calcd. for  $\text{C}_{15}\text{H}_{12}\text{OH}^+$ : 209.0961. Found 209.0932 ( $\text{MH}^+$ ); FT-IR (neat) 3048, 2981, 2949, 2919, 1588, 1508, 1392, 1023,  $770\text{ cm}^{-1}$

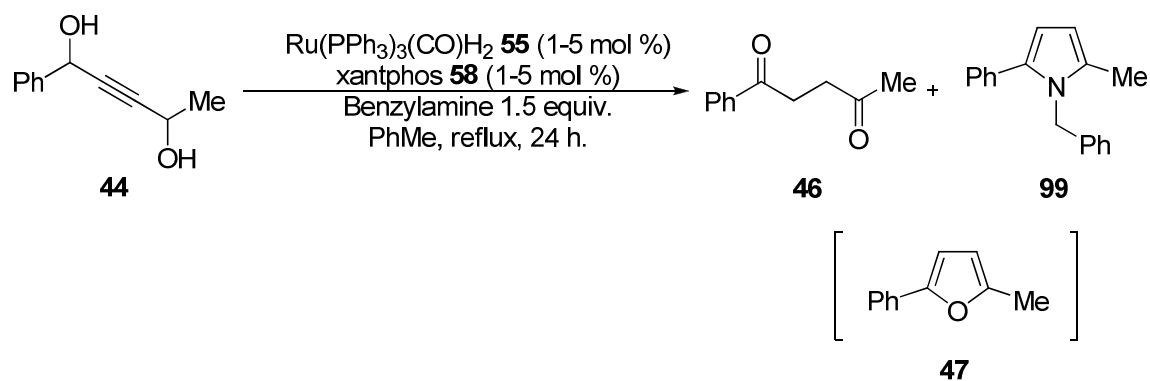
**97**

**5-Methyl-2,2'-bifuran 97** (Table 8, entry 19). According to the general procedure using 1-(Furan-2-yl)pent-2-yne-1,4-diol (**77**, 322 mg, 2 mmol) 5-methyl-2,2'-bifuran **97** was synthesised. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion with 29% furan.

**98**

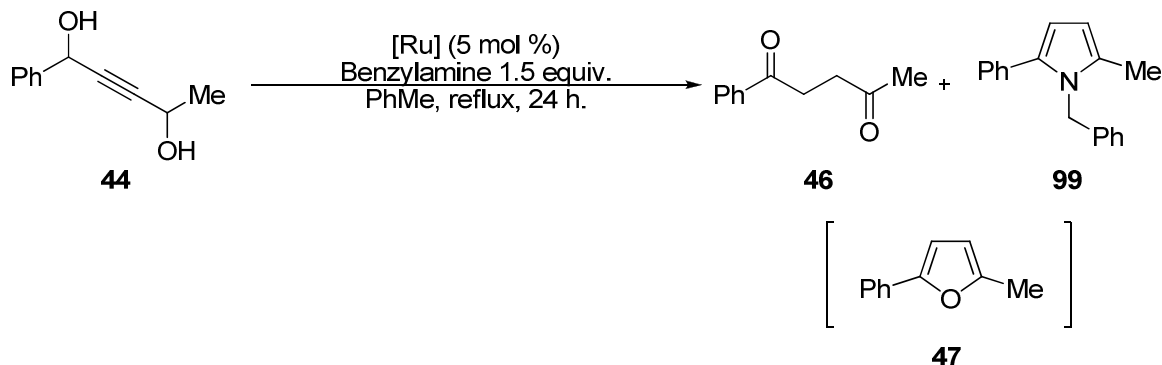
**2-Methyl-5-(thiophen-2-yl)furan 98<sup>4</sup>** (Table 8 entry 20). According to the general procedure using 1-(thiophen-2-yl)pent-2-yne-1,4-diol (**78**, 364 mg, 2 mmol) 2-methyl-5-(thiophen-2-yl)furan **98** was synthesised. The crude reaction mixture was purified by column chromatography (hexane,  $R_f = 0.70$ ) and the title compound was afforded as a clear oil (126 mg, 38%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 7.25$  (t, 1H,  $J = 2.0$  Hz), 7.14 (m, 2H), 6.21 (d, 1H,  $J = 3.2$  Hz), 5.87 (m, 1H), 2.20 (s, 3H); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 151.66, 149.96, 133.41, 126.46, 125.32, 118.23, 107.75, 106.34, 14.09$ .

## 5.3.1 Experimental Procedures: Chapter 3

5.3.4 Procedure for initial formation of pyrrole *via* isomerisation and cyclisation in the presence of benzylamine.

To an oven dried, argon purged Young's tap carousel tube was charged 1-phenylpent-2-yne-1,4-diol (**44**, 352 mg, 2 mmol),  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 18.3, 91.5 mg, 0.01 mmol, 0.05 mmol, 0.01 equiv, 0.05 equiv.), xantphos (**58**, 11.5, 57.5 mg, 0.01 mmol, 0.05 mmol, 0.01 equiv, 0.05 equiv.) and benzylamine (136  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv.) Degassed anhydrous toluene (1 mL) was added and the reaction heated to reflux for 24 hours. The solvent was removed *in vacuo* and the crude reaction mixture analysed by  $^1\text{H}$  NMR spectroscopy. Conversions was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46**, 1-benzyl-2-methyl-5-phenyl-1H-pyrrole **99** and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### 5.3.4 Comparison of ruthenium catalysts

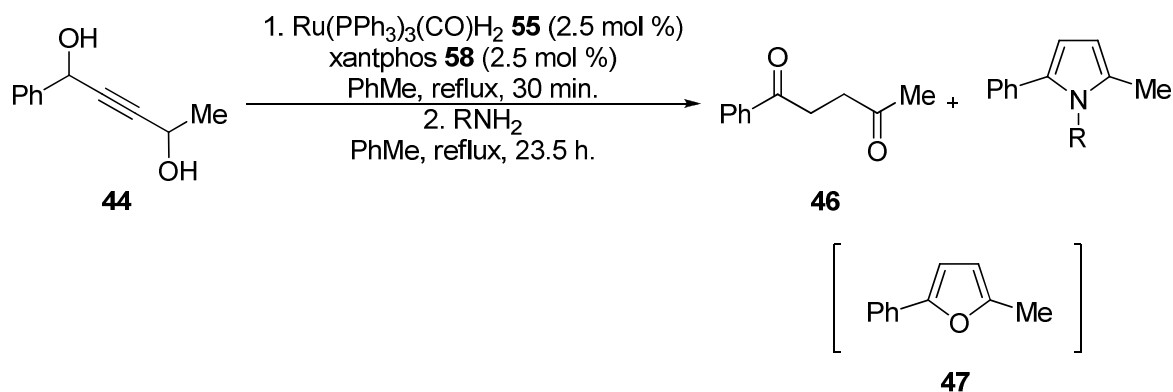


To an oven dried, argon purged Young's tap carousel tube was charged 1-phenylpent-2-yne-1,4-diol (**44**, 176 mg, 1 mmol), with metal catalysts **15-58** and caesium carbonate (10 mol %, equimolar with respect to chloride in the appropriate systems). The solvent was removed *in vacuo* and the crude reaction mixture analysed by  $^1\text{H}$  NMR spectroscopy. Conversion as illustrated in **Table 9**, were determined by analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46**, 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole **99** and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

### 5.3.5 Optimisation: Catalyst loading

To an oven dried, argon purged Young's tap carousel tube was charged 1-phenylpent-2-yne-1,4-diol (**44**, 176 mg, 1 mmol),  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  (**58**, 1-5 mol%, **Table 10**, entries **1-3**), xantphos (**58**, 1-5 mol%) and benzylamine (136  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv.) Degassed anhydrous toluene (1 mL) was added and the reaction heated to reflux for 24 hours. The solvent was removed *in vacuo* and the crude reaction mixture analysed by  $^1\text{H}$  NMR spectroscopy. Conversions as shown in **Table 10** were determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46**, 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole **99** and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

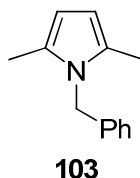
## 5.3.6 Optimisation: Amine loading



To an oven dried, argon purged Young's tap carousel tube was charged with 1-phenylpent-2-yne-1,4-diol (**44**, 176 mg, 1 mmol),  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.4 mg, 0.025 mmol, 0.025 equiv.) and degassed, anhydrous toluene (1 mL). The reaction was heated at reflux to pre-form the active catalytic species. After 30 minutes benzylamine **100** or 2-phenethylamine **101** was added (1-3 mmol, 1-3 equiv., **Table 11**, **entries 1-6**) and the reaction then was heated at reflux for a total of 23.5 hours. The solvent was removed *in vacuo* and the crude reaction mixture analysed by  $^1\text{H}$  NMR spectroscopy. Conversions as shown in **Table 11** were determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **46**, pyrrole and 1-phenyl-5-methyl furan **47** in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

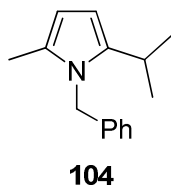
### 5.3.7 Synthesis of *N*-2,5-substituted pyrroles via an isomerisation cyclocondensation tandem reaction

#### Representative procedure

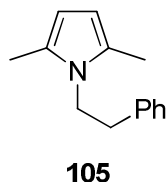


**1-Benzyl-2,5-dimethyl-1*H*-pyrrole 103<sup>5</sup>** (Table 12, entry 1). To an oven dried, argon purged Young's tap carousel tube was charged with 3-hexyn-2,5-diol (**41**, 114 mg, 1 mmol), Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv), xantphos (**58**, 14.4 mg, 0.025 mmol, 0.025 equiv.) and degassed anhydrous toluene (1 mL). The reaction was heated at reflux to preform the active catalytic species. After 30 minutes benzylamine (**100**, 218  $\mu$ L, 2 mmol, 2 equiv.) and the reaction heated at reflux for a total of 24 hours. The solvent was removed *in vacuo* and the crude reaction mixture was analysed by GC-MS. GC-MS analysis showed 100% conversion with 100% 1-benzyl-2,5-dimethyl-1*H*-pyrrole **103** formation. GC-MS retention time 15.12 min., *m/z* (EI) 186 (MH<sup>+</sup>). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether, *R<sub>f</sub>* = 0.30) and the title compound was afforded as a pale yellow oil (279 mg, 76%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 7.19 (m, 3H), 6.81 (d, 2H, *J* = 7.1 Hz), 5.78 (s, 2H), 4.93 (s, 2H), 2.06 (s, 6H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 138.94, 129.09, 128.40, 127.38, 126.04, 105.77, 47.10, 12.82; HRMS(ESI-TOF): calcd. for C<sub>13</sub>H<sub>15</sub>NH<sup>+</sup>: 186.1277. Found 186.1269 (MH<sup>+</sup>)

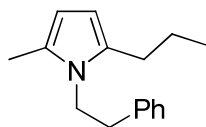




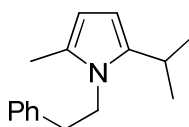
**1-Benzyl-2-isopropyl-5-methyl-1H-pyrrole 104** (Table 12, entry 2) According to the representative procedure using 6-methylhept-3-yne-2,5-diol (**61**, 142 mg, 1 mmol) and benzylamine (**100**, 218  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 95% 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole **104** formation. GC-MS retention time 16.09 min.,  $m/z$  (EI) 214 ( $MH^+$ ).



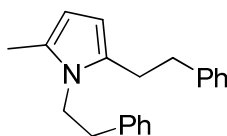
**2,5-Dimethyl-1-phenethyl-1H-pyrrole 105**<sup>6</sup> (Table 12, entry 3). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and 2-phenethylamine (**101**, 503  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 100% 2,5-dimethyl-1-phenethyl-1H-pyrrole **105** formation. GC-MS retention time 16.40 min.,  $m/z$  (EI) 200 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C):diethyl ether,  $R_f$  = 0.36) and the title compound was afforded as a pale yellow oil (336.6 mg, 84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$  = 7.19 (m, 3H), 7.02 (m, 2H), 5.69 (s, 2H), 3.87 (t, 2H,  $J$  = 7.6 Hz), 2.80 (t, 2H,  $J$  = 7.6 Hz), 2.07 (s, 6H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$  = 138.96, 129.24, 129.01, 127.76, 127.03, 105.58, 45.67, 37.95, 12.75; HRMS(ESI-TOF): calcd. for C<sub>13</sub>H<sub>15</sub>NH<sup>+</sup>: 200.1439, C<sub>14</sub>H<sub>17</sub>NNa<sup>+</sup>, 222.1258. Found 200.1434 ( $MH^+$ ), 222.1263 (MNa<sup>+</sup>).

**106**

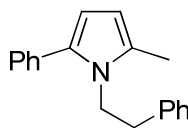
**2-Methyl-1-phenethyl-5-propyl-1H-pyrrole 106 (Table 12, entry 4)** According to the representative procedure using oct-3-yne-2,5-diol (**60**, 142 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 86% 2-methyl-1-phenethyl-5-propyl-1H-pyrrole **106** formation. GC-MS retention time 17.80 min.,  $m/z$  (EI) 228 ( $MH^+$ ).

**107**

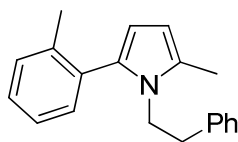
**2-Isopropyl-5-methyl-1-phenethyl-1H-pyrrole 107 (Table 12, entry 5).** According to the representative procedure using 6-methylhept-3-yne-2,5-diol (**61**, 142 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 65% 2-isopropyl-5-methyl-1-phenethyl-1H-pyrrole **107** formation. GC-MS retention time 17.26 min.,  $m/z$  (EI) 228 ( $MH^+$ ).

**108**

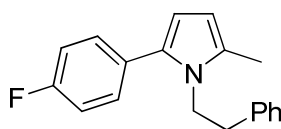
**2-Methyl-1,5-diphenethyl-1H-pyrrole 108 (Table 12, entry 6).** According to the representative procedure using 7-Phenylhept-3-yne-2,5-diol (**63**, 204 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 71% 2-methyl-1,5-diphenethyl-1H-pyrrole **108** formation. GC-MS retention time 22.40 min.,  $m/z$  (EI) 290 ( $MH^+$ ).

**109**

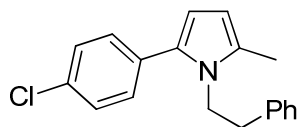
**2-Methyl-1-phenethyl-5-phenyl-1H-pyrrole 109 (Table 12, entry 7).** According to the representative procedure using 1-phenylpent-2-yne-1,4-diol (**44**, 176 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 86% 2-methyl-1-phenethyl-5-phenyl-1H-pyrrole **109** formation. GC-MS retention time 20.78 min.,  $m/z$  (EI) 262 ( $MH^+$ ).

**110**

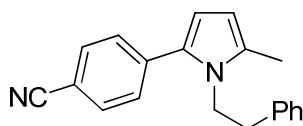
**2-Methyl-1-phenethyl-5-*o*-tolyl-1*H*-pyrrole 110** (Table 12, entry 8). According to the representative procedure using 1-*o*-tolylpent-2-yne-1,4-diol (**71**, 190 mg, 1 mmol), and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 71% 2-methyl-1-phenethyl-5-*o*-tolyl-1*H*-pyrrole **110** formation. GC-MS retention time 20.69 min.,  $m/z$  (EI) 276 ( $MH^+$ ).

**111**

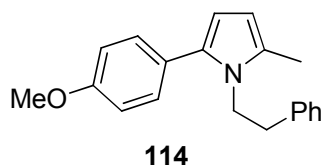
**2-(4-Fluorophenyl)-5-methyl-1-phenethyl-1*H*-pyrrole 111** (Table 12, entry 9). According to the representative procedure using 1-(4-Fluorophenyl)pent-2-yne-1,4-diol (**72**, 194 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 66% 2-(4-fluorophenyl)-5-methyl-1-phenethyl-1*H*-pyrrole **111** formation. GC-MS retention time 20.56 min.,  $m/z$  (EI) 280 ( $MH^+$ ).

**112****2-(4-Chlorophenyl)-5-methyl-1-phenethyl-1H-pyrrole 112 (Table 12, entry 10).**

According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 70% 2-(4-chlorophenyl)-5-methyl-1-phenethyl-1H-pyrrole **112** formation. GC-MS retention time 22.19 min.,  $m/z$  (EI) 296 ( $\text{MH}^+$ ).

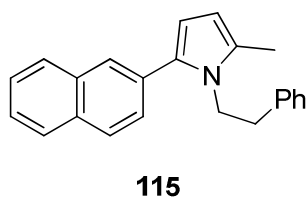
**113****4-(5-Methyl-1-phenethyl-1H-pyrrol-2-yl)benzonitrile 113 (Table 12, entry 11).**

According to the representative procedure using 4-(1,4-Dihydroxypent-2-ynyl)benzonitrile (**73**, 201 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 91% 4-(5-methyl-1-phenethyl-1H-pyrrol-2-yl)benzonitrile **113** formation. GC-MS retention time 23.47 min.,  $m/z$  (EI) 296 ( $\text{MH}^+$ ).



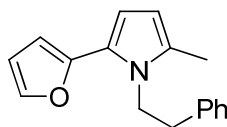
**2-(4-Methoxyphenyl)-5-methyl-1-phenethyl-1H-pyrrole 114 (Table 12, entry 12).**

According to the general procedure using 1-(4-Methoxyphenyl)pent-2-yne-1,4-diol (**74**, 412 mg, 2 mmol) an attempt to synthesis 2-(4-Methoxyphenyl)-5-methyl-1-phenethyl-1H-pyrrole **114** failed. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy showed 100% conversion but with 60% diketone and 29% furan side products.



**2-Methyl-5-(naphthalen-2-yl)-1-phenethyl-1H-pyrrole 115 (Table 12, entry 13).**

According to the representative procedure using 1-(naphthalen-2-yl)pent-2-yne-1,4-diol (**76**, 226 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 70% 2-methyl-5-(naphthalen-2-yl)-1-phenethyl-1H-pyrrole **115** formation. GC-MS retention time 23.95 min.,  $m/z$  (EI) 312 ( $\text{MH}^+$ ).

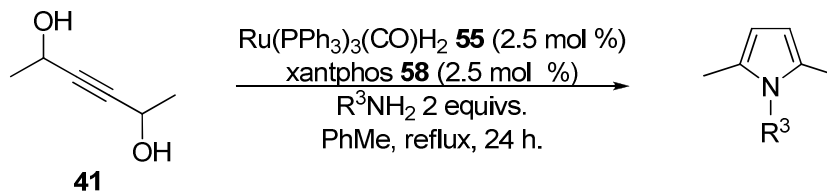
**116**

**2-(Furan-2-yl)-5-methyl-1-phenethyl-1H-pyrrole 116** (Table 12, entry 14).

According to the representative procedure using 1-(Furan-2-yl)pent-2-yne-1,4-diol (**77**, 161 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS showing 100% conversion with 86% 2-(furan-2-yl)-5-methyl-1-phenethyl-1H-pyrrole **116** formation. GC-MS retention time 19.61 min.,  $m/z$  (EI) 252 ( $\text{MH}^+$ ).

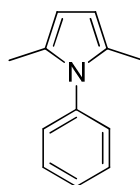
### 5.3.8 Synthesis of *N*-2,5-Substituted Pyrroles: Amine Scope

#### Representative procedure.

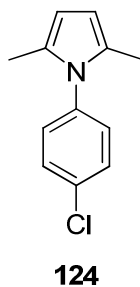


To an oven dried, argon purged Young's tap carousel tube was charged with 3-hexyn-2,5-diol (**41**, 114 mg, 2 mmol),  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.4 mg, 0.025 mmol, 0.025 equiv.) and degassed anhydrous toluene (2 mL). The reaction was heated at reflux to pre-form the active catalytic species. After 30 minutes amines **117-122** (4 mmol, 2 equiv., **Table 13 entries 1-8**) were added and the reaction heated at reflux for a total of 23.5 hours. The solvent was removed *in vacuo* and the crude reaction mixture was analysed by GC-MS

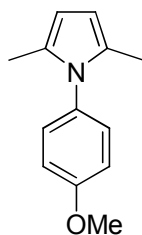


**123**

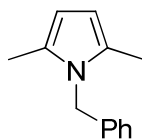
**2,5-Dimethyl-1-phenyl-1*H*-pyrrole 123<sup>5</sup>** (Table 13, entry 1). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and aniline (**117**, 364  $\mu$ L, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 76% 2,5-dimethyl-1-phenyl-1*H*-pyrrole **123** formation. GC-MS retention time 13.59 min.,  $m/z$  (EI) 171 ( $M^+$ ), 172 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.37) and the title compound was afforded as a pale yellow oil (212 mg, 63%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 7.32 (m, 3H), 7.13 (m, 2H), 5.82 (s, 2H), 1.95 (s, 6H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 139.43, 129.44, 129.20, 128.66, 128.02, 106.04, 13.40.



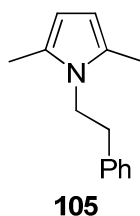
**1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole 124<sup>6</sup>** (Table 13, entry 2). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and 4-chloroaniline (**118**, 510 mg, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 72% 1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole **124** formation. GC-MS retention time 15.52 min.,  $m/z$  (EI) 205 ( $M^+$ ), 206 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.39) and the title compound was afforded as a pale yellow oil (353 mg, 86%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 7.36 (d, 2H,  $J$  = 8.6 Hz), 7.08 (d, 2H,  $J$  = 8.6 Hz), 5.82 (s, 2H), 1.94 (s, 6H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 137.93, 133.93, 129.90, 129.70, 129.13, 106.43, 13.35. HRMS(ESI-TOF): calcd. for  $C_{12}H_{12}NClH^+$ : 206.0731. Found 206.0714 ( $MH^+$ ).

**125**

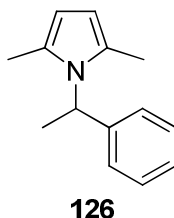
**1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole 125<sup>5</sup>** (Table 13, entry 3). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and 4-methoxyaniline (**120**, 492 mg, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 98% 1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole **125** formation. GC-MS retention time 16.27 min., m/z (EI) 201 ( $M^+$ ), 202 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.28) and the title compound was afforded as a pale yellow oil (249 mg, 61%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{ppm}$  = 7.04 (d, 2H,  $J$  = 8.9 Hz), 6.89 (d, 2H,  $J$  = 8.9 Hz), 5.80 (s, 2H), 3.78 (s, 3H), 1.94 (s, 6H); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{ppm}$  = 159.27, 132.17, 129.62, 129.43, 114.60, 105.65, 55.85, 13.34; HRMS(ESI-TOF): calcd. for C<sub>13</sub>H<sub>15</sub>NOH<sup>+</sup>: 202.1231. Found 202.1218 ( $MH^+$ ).

**103**

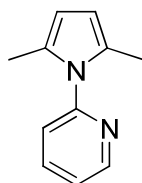
**1-Benzyl-2,5-dimethyl-1H-pyrrole 103<sup>6</sup>** (Table 12 and 13, entries 1 and 5). According to the general procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and benzylamine (**100**, 437  $\mu$ L, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 100% 1-benzyl-2,5-dimethyl-1H-pyrrole **103** formation. GC-MS retention time 15.12 min.,  $m/z$  (EI) 186 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.30) and the title compound was afforded as a pale yellow oil (279 mg, 76%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{ppm}$  = 7.19 (m, 3H), 6.81 (d, 2H,  $J$  = 7.1 Hz), 5.78 (s, 2H), 4.93 (s, 2H), 2.06 (s, 6H); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{ppm}$  = 138.94, 129.09, 128.40, 127.38, 126.04, 105.77, 47.10, 12.82; HRMS(ESI-TOF): calcd. for  $C_{13}H_{15}NH^+$ : 186.1277. Found 186.1269 ( $MH^+$ ).



**2,5-Dimethyl-1-phenethyl-1H-pyrrole 105<sup>6</sup>** (Tables 12 and 13, entries 3 and 6). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and 2-phenethylamine (**101**, 504  $\mu$ L, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 100% 2,5-dimethyl-1-phenethyl-1H-pyrrole **105** formation. GC-MS retention time 16.40 min.,  $m/z$  (EI) 200 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.36) and the title compound was afforded as a pale yellow oil (336.6 mg, 84%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 7.19 (m, 3H), 7.02 (m, 2H), 5.69 (s, 2H), 3.87 (t, 2H,  $J$  = 7.6 Hz), 2.80 (t, 2H,  $J$  = 7.6 Hz), 2.07 (s, 6H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 138.96, 129.24, 129.01, 127.76, 127.03, 105.58, 45.67, 37.95, 12.75; HRMS(ESI-TOF): calcd. for  $C_{13}H_{15}NH^+$ : 200.1439,  $C_{14}H_{17}NNa^+$ , 222.1258. Found 200.1434 ( $MH^+$ ), 222.1263 ( $MNa^+$ ).



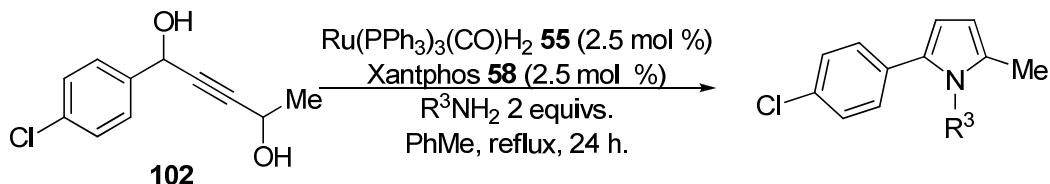
**2,5-Dimethyl-1-(1-phenylethyl)-1H-pyrrole 126<sup>6</sup>** (Table 13, entry 7). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 228 mg, 2 mmol) and 1-phenethylamine (**121**, 516  $\mu$ L, 4 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 99% 2,5-dimethyl-1-(1-phenylethyl)-1H-pyrrole **126** formation. GC-MS retention time 15.73 min.,  $m/z$  (EI) 200 ( $MH^+$ ). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 Petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.59) and the title compound was afforded as a pale yellow oil (215 mg, 54%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 7.20 (m, 3H), 6.96 (d, 2H,  $J$  = 7.1 Hz), 5.72 (s, 2H), 5.39 (q, 1H,  $J$  = 7.1 Hz), 2.00 (s, 6H), 1.78 (d, 3H,  $J$  = 7.1 Hz);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta_{ppm}$  = 142.85, 128.86, 128.69, 127.22, 126.42, 106.50, 52.86, 19.71, 14.22; HRMS(ESI-TOF): calcd. for  $C_{14}H_{17}NH^+$ : 200.1434. Found 200.1420 ( $MH^+$ ).

**127**

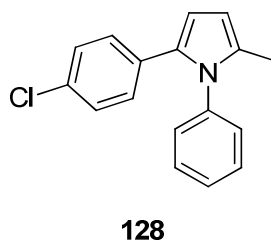
**2-(2,5-Dimethyl-1H-pyrrol-1-yl)pyridine 127** (Table 13, entry 8). According to the representative procedure using 3-hexyn-2,5-diol (**41**, 114 mg, 1 mmol) and 2-aminopyridine (**122**, 188 mg, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 33% 2-(2,5-dimethyl-1H-pyrrol-1-yl)pyridine **127** formation. GC-MS retention time 14.76 min., m/z (EI) 172 ( $M^+$ ), 173 ( $MH^+$ ).

5.3.8 Synthesis of *N*-2,5-Substituted Pyrroles: Amine Scope II

## Representative procedure

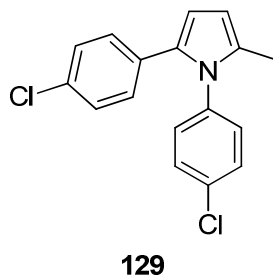


To an oven dried, argon purged Young's tap carousel tube was charged 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol), Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.4 mg, 0.025 mmol, 0.025 equiv.) and degassed anhydrous toluene (1 mL). The reaction was heated at reflux to perform the active catalytic species. After 30 minutes amines **117-125** (2 mmol, **Table 14**, **entries 1-11**) were added and the reaction heated at reflux for a total of 24 hours. The solvent was removed *in vacuo* and the crude reaction mixture was analysed by GC-MS

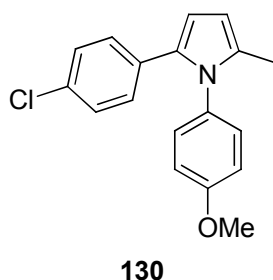


**2-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrrole 128** (**Table 14**, **entry 1**). According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and aniline (**117**, 182  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 33% 2-(4-chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrrole **128** formation. GC-MS retention time 20.46 min., *m/z* (EI) 268 (MH<sup>+</sup>).

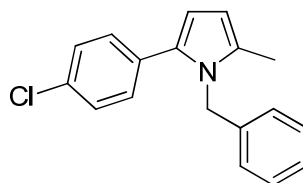




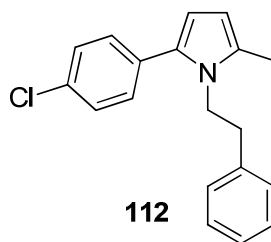
**1,2-Bis(4-chlorophenyl)-5-methyl-1H-pyrrole 129** (Table 14, entry 2). According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 4-chloroaniline (**118**, 255 mg, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 19% 1,2-bis(4-chlorophenyl)-5-methyl-1H-pyrrole **129** formation. GC-MS retention time 21.78min., m/z (EI) 302 (MH<sup>+</sup>).



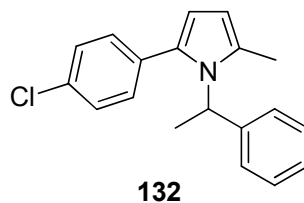
**2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1H-pyrrole 130** (Table 14, entry 3). According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 4-methoxyaniline (**120**, 255 mg, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 50% 2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1H-pyrrole **130** formation. GC-MS retention time 22.24 min., m/z (EI) 298 (MH<sup>+</sup>).

**131**

**1-Benzyl-2-(4-chlorophenyl)-5-methyl-1H-pyrrole 131** (Table 14, entry 4). According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and benzylamine (**100**, 218  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 70% 1-benzyl-2-(4-chlorophenyl)-5-methyl-1H-pyrrole **131** formation. GC-MS retention time 21.41 min.,  $m/z$  (EI) 282 ( $\text{MH}^+$ ).

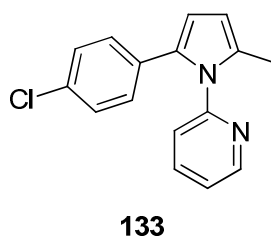
**112**

**2-(4-Chlorophenyl)-5-methyl-1-phenethyl-1H-pyrrole 112** (Tables 12 and 14, entries 5 and 10). According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 2-phenethylamine (**101**, 251  $\mu\text{L}$ , 2 mmol, 2 equiv.) The title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 70% 2-(4-chlorophenyl)-5-methyl-1-phenethyl-1H-pyrrole **112** formation. GC-MS retention time 22.16 min.,  $m/z$  (EI) 296 ( $\text{MH}^+$ ).



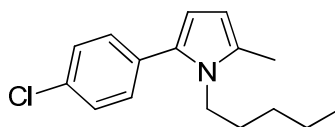
**2-(4-Chlorophenyl)-5-methyl-1-(1-phenylethyl)-1H-pyrrole 132 (Table 14, entry 6).**

According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 1-phenethylamine (**121**, 257  $\mu$ L, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 67% 2-(4-chlorophenyl)-5-methyl-1-(1-phenylethyl)-1H-pyrrole **132** formation. GC-MS retention time 21.68 min.,  $m/z$  (EI) 296 ( $MH^+$ ).

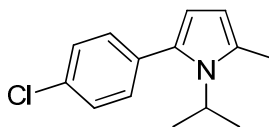


**2-(2-(4-chlorophenyl)-5-methyl-1H-pyrrol-1-yl)pyridine 133 (Table 14, entry 7).**

According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 2-aminopyridine (**122**, 188 mg, 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 2% 2-(2-(4-chlorophenyl)-5-methyl-1H-pyrrol-1-yl)pyridine **133** formation. GC-MS retention time 20.98 min.,  $m/z$  (EI) 269 ( $MH^+$ ).

**134****2-(4-Chlorophenyl)-5-methyl-1-pentyl-1H-pyrrole 134 (Table 14, entry 8).**

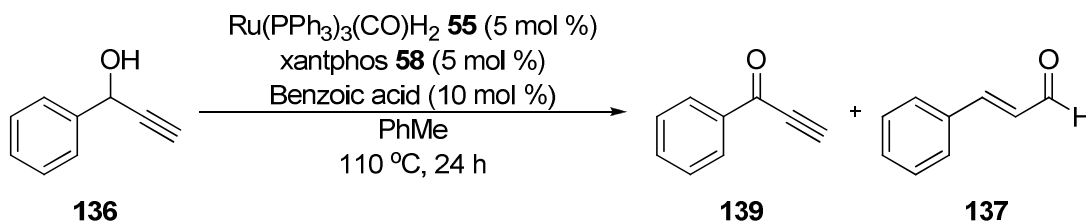
According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 1-aminopentane (**123**, 231  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 55% 2-(4-Chlorophenyl)-5-methyl-1-pentyl-1H-pyrrole **134** formation. GC-MS retention time 19.21 min.,  $m/z$  (EI) 262 ( $\text{MH}^+$ ).

**135****2-(4-Chlorophenyl)-1-isopropyl-5-methyl-1H-pyrrole 135 (Table 14, entry 9).**

According to the representative procedure using 1-(4-chlorophenyl)pent-2-yne-1,4-diol (**102**, 210 mg, 1 mmol) and 2-isopropylamine (**124**, 171  $\mu\text{L}$ , 2 mmol, 2 equiv.) the title compound was synthesised. The crude reaction mixture was analysed by GC-MS which showed 100% conversion with 27% 2-(4-Chlorophenyl)-1-isopropyl-5-methyl-1H-pyrrole **135** formation. GC-MS retention time 17.46 min.,  $m/z$  (EI) 234 ( $\text{MH}^+$ ).

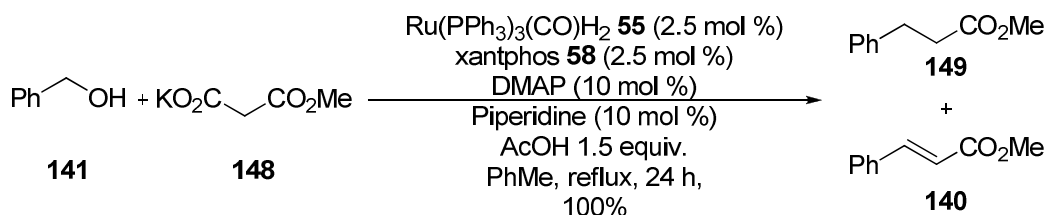
## 5.4 Experimental Procedures: Chapter 4

## 5.4.3 Procedure for attempted isomerisation of propargylic alcohols



To oven dried, argon purged Radley's carousel tubes containing Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 45.8 mg, 0.05 mmol, 0.05 equiv.), xantphos (**58**, 29 mg, 0.05 mmol, 0.05 equiv.) and benzoic acid (6.1 mg, 0.01 mmol, 0.01 equiv.) was added 1-phenyl-2-propyn-1-ol (**136**, 125.1  $\mu$ L, 1 mmol) and toluene (1 mL). The reaction was heated at reflux for 24 hours. On completion the reaction was allowed to cool and toluene was removed *in vacuo* and the crude reaction mixture was analysed by <sup>1</sup>H NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2-propyn-1-ol **136**, 1-phenyl-2-propyn-1-one **139** and cinnamaldehyde **137**.

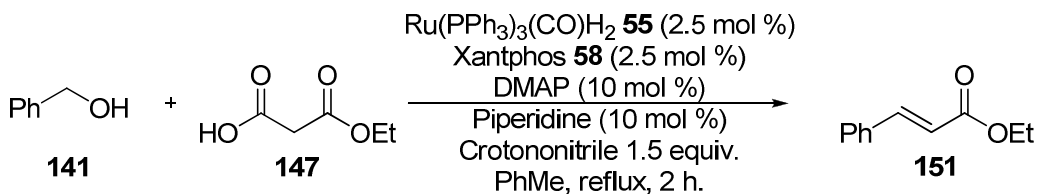
#### 5.4.6 Procedure for initial studies into a decarboxylative Knoevenagel condensation on alcohols.



To oven dried, argon purged Radley's carousel tubes containing  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.5 mg, 0.025 mmol, 0.025 equiv.) DMAP (12.2 mg, 0.01 mmol, 0.01 equiv.) and piperidine (9.8  $\mu\text{L}$ , 0.01 mmol, 0.01 equiv.) was added toluene (1 ml), benzyl alcohol (109  $\mu\text{L}$ , 1 mmol, 1 equiv.), methyl potassium malonate (234 mg, 1.5 mmol, 1.5 equiv) and acetic acid (85.8  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv). The reactions were heated to reflux for 24 hours, cooled to room temperature and the solvent was removed *in vacuo*. and the crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydromethyl cinnamate **149** and methyl cinnamate **140**.

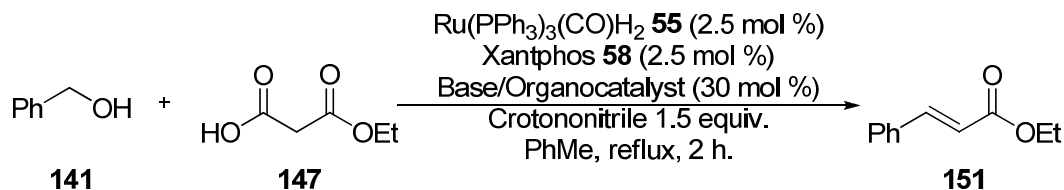
### 5.4.7 Optimisation of tandem hydrogen transfer and condensation

#### Procedure for model tandem hydrogen transfer and condensation



To oven dried, argon purged Radley's carousel tubes containing  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, (22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.5 mg, 0.025 mmol, 0.025 equiv.) DMAP (12.2 mg, 0.01 mmol, 0.01 equiv.), piperidine (9.8  $\mu\text{L}$ , 0.01 mmol, 0.01 equiv.) and crotononitrile (122  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv.) was added toluene (1 ml), benzyl alcohol (109  $\mu\text{L}$ , 1 mmol, 1 equiv.) and mono ethyl malonate (**147**, 129.8  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv.). The reactions were heated at reflux for 2 hours, cooled to room temperature and the solvent was removed *in vacuo*. The crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydroethyl cinnamate **169** and ethyl cinnamate **151**.

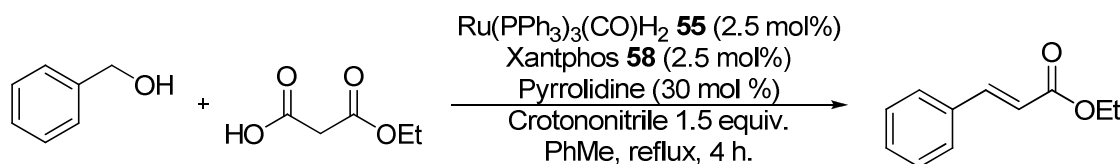
## Base screen for tandem hydrogen transfer and condensation



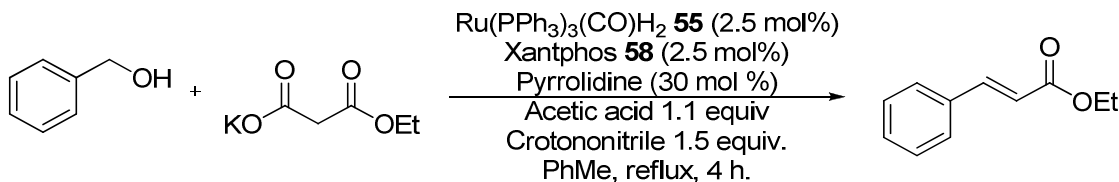
To oven dried, argon purged Radley's carousel tubes containing  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, (22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.5 mg, 0.025 mmol, 0.025 equiv.) Base/organocatalyst (30 mol % and shown in **Table 15**) and crotononitrile (122  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv.) was added toluene (1 ml), benzyl alcohol (109  $\mu\text{L}$ , 1 mmol, 1 equiv.) and mono ethyl malonate (**147**, 129.8  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv). The reactions were heated at reflux for 2 hours, cooled to room temperature and the solvent was removed *in vacuo*. The crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydroethyl cinnamate **169** and ethyl cinnamate **151**.



### 5.4.8 Representative procedures for the addition of malonates to alcohols *via* tandem hydrogen transfer and condensation

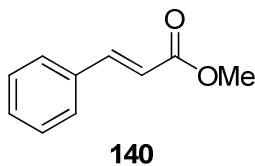


**Procedure A:** To oven dried, argon purged Radley's carousel tubes containing  $\text{Ru(PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), xantphos (**58**, 14.5 mg, 0.025 mmol, 0.025 equiv.) and pyrrolidine (25  $\mu\text{L}$ , 0.30 mmol, 0.30 equiv.) was added toluene (1 ml), benzyl alcohol (109  $\mu\text{L}$ , 1 mmol, 1 equiv.), crotononitrile (122  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv.) and monoethyl malonate (**147**, 145.25  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv.). The reactions were heated at reflux for 2 hours, cooled to room temperature and the solvent was removed *in vacuo*. The resultant oil was purified by column chromatography.

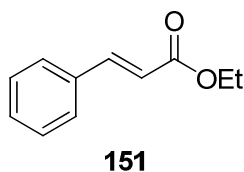


**Procedure B:** As for procedure A except methyl potassium malonate (160mg, 1.1 mmol, 1.1 equiv) or ethyl potassium malonate (187mg, 1.1 mmol, 1.1 equiv) were used. Acetic acid (59  $\mu\text{L}$ , 1.1 mmol 1.1equiv) was also added. The crude mixture was dissolved in ether, washed with sat. Ammonium chloride, sat. sodium carbonate, water and dried over magnesium sulfate. The product was concentrated *in vacuo* and purified by column chromatography.

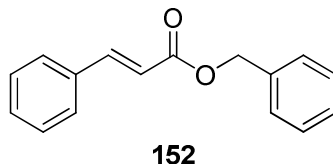
#### 5.4.8 Synthesis of $\alpha,\beta$ -unsaturated esters by a tandem hydrogen transfer condensation reaction



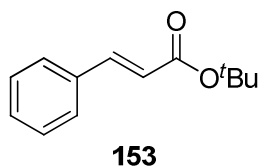
**(E)-Methyl cinnamate 140**<sup>7</sup> (Table 16, entry 1). According to the representative **procedure B** using benzyl alcohol (436  $\mu$ L, 4 mmol, 1 equiv.), methyl potassium malonate (640 mg, 4.4 mmol, 1.1 equiv.) and acetic acid (236  $\mu$ L, 4.4 mmol, 1.1 equiv) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.44) affording the product as a white solid (485 mg, 74%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.65 (d, 1H,  $J$  = 15.9 Hz), 7.54-7.36 (m, 5H), 6.46 (d, 1H,  $J$  = 15.9 Hz), 3.8 (s, 3H); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 167.3, 144.8, 134.2, 130.2, 128.8, 128.0, 117.7, 51.6.



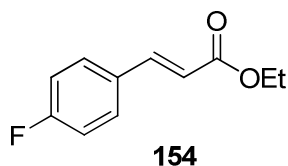
**(E)-Ethyl cinnamate 151**<sup>7</sup> (Table 16, entry 2 and 3). According to the representative **procedure B** using benzyl alcohol (436  $\mu$ L, 4 mmol, 1 equiv.), ethyl potassium malonate (749 mg, 4.4 mmol, 1.1 equiv.) and acetic acid (236  $\mu$ L, 4.4 mmol, 1.1 equiv). The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.31) affording the product as a pale yellow oil (502mg, 71%). Using **procedure A** with mono-ethyl malonate (581  $\mu$ L 4.4 mmol, 1.1 equiv). The title compound was obtained as above. (679.5 mg, 95%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 7.70 (d, 1H,  $J$  = 15.9 Hz), 7.55-7.36 (m, 5H), 6.45 (d, 1H,  $J$  = 15.9 Hz), 4.27 (q, 2H,  $J$  = 7.2 Hz), 1.35 (t, 3H,  $J$  = 7.2 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 166.9, 144.5, 130.1, 128.8, 127.9, 118.2, 60.4, 14.2; HRMS(ESI-TOF): calcd. for C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>Na<sup>+</sup>: 199.0734. Found 199.0724 (MNa<sup>+</sup>); FT IR (film). 2981, 1711, 1638, 1578, 1496, 1450, 1366, 1311, 1270, 1201, 1139, 980, 768 cm<sup>-1</sup>



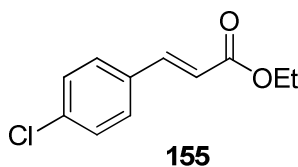
**(E)-Benzyl cinnamate 152**<sup>7</sup> (Table 16, entry 4). According to the representative **procedure A** using benzyl alcohol (436  $\mu$ L, 4 mmol, 1 equiv.), and mono-benzyl malonate (854.4 mg, 4.4 mmol, 1.1 equiv) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.41) affording the product as a clear oil (802 mg, 84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 7.45 (d, 1H,  $J$  = 15.9 Hz), 7.28-7.0 (m, 10H), 6.23 (d, 1H,  $J$  = 15.9 Hz), 4.99 (s, 2H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta_{\text{ppm}}$  = 166.7, 145.1, 136.0, 134.3, 130.3, 128.8, 128.5, 128.2, 128.0, 117.8, 66.3.



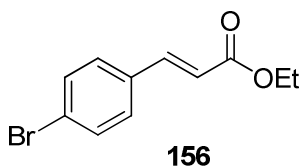
**(E)-tert-Butyl cinnamate 153<sup>8</sup>** (Table 16, entry 5). According to the representative **procedure A** using benzyl alcohol (436  $\mu$ L, 4 mmol, 1 equiv.), and mono-*tert*-butyl malonate (650  $\mu$ L, 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.46) affording the product as a clear oil (575mg, 71%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.60 (d, 1H,  $J$  = 16.2 Hz), 7.53-7.35 (m, 5H), 6.37 (d, 1H,  $J$  = 16.2 Hz), 1.55 (s, 9H); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 166.3, 143.5, 134.7, 129.9, 128.8, 127.9, 120.2, 80.5, 28.2; HRMS(ESI-TOF): calcd. for C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>Na<sup>+</sup>: 227.1047. Found 227.1030 (MNa<sup>+</sup>); FT IR (film). 2978, 2932, 1711, 1638, 1578, 1496, 1475, 1450, 1329, 1284, 1256, 1207, 1148, 979, 871, 768, 711, 685 cm<sup>-1</sup>



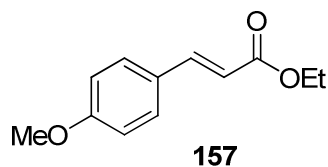
**Ethyl (E)-3-(4-fluorophenyl)-2-propanoate 154<sup>7</sup>** (Table 16, entry 6). According to the representative **procedure A** using 4-fluoro benzyl alcohol (431 $\mu$ L, 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu$ L, 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.35) affording the product as a pale yellow oil (675mg, 87%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.65 (d, 1H,  $J$  = 15.9 Hz), 7.53 (d, 1H  $J$  = 5.7 Hz), 7.5 (d, 1H  $J$  = 5.7 Hz) 7.07 (ps-t, 2H,  $J$  = 8.7Hz), 6.5 (d, 1H,  $J$  = 15.9 Hz), 4.26 (q, 2H,  $J$  = 7.2 Hz), 1.34 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 166.8, 163.8 (d,  $^1J_{\text{CF}}$  = 250 Hz), 143.2, 130.6 (d,  $^4J_{\text{CF}}$  = 3.4 Hz), 129.8 (d,  $^3J_{\text{CF}}$  = 8.4 Hz), 118.0 (d,  $^5J_{\text{CF}}$  = 2.3 Hz), 116.0 (d,  $^2J_{\text{CF}}$  = 21.7 Hz), 60.5, 14.3; FT-IR (thin film). 2991, 1888, 1711, 1640, 1601, 1510, 1415, 1367, 1310, 1281, 1233, 1160, 1096, 1034, 985, 828 cm<sup>-1</sup>



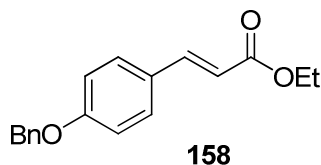
**Ethyl (*E*)-3-(4-chlorophenyl)-2-propenoate 155<sup>9</sup>** (Table 16, entry 7). According to the representative **procedure A** using 4-chloro benzyl alcohol (431  $\mu$ L, 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu$ L, 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.35) affording the product as a pale yellow oil (770mg, 91%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.63 (d, 1H,  $J$  = 15.9 Hz), 7.44 (d, 2H  $J$  = 8.4 Hz), 7.35 (d, 2H,  $J$  = 8.4 Hz), 6.40 (d, 2H,  $J$  = 15.9 Hz), 4.27 (q, 2H,  $J$  = 7.2 Hz), 1.34 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 166.6, 143.0, 136.0, 132.9, 129.1, 128.5, 118.8, 60.6, 14.2; FT-IR (thin film). 2982, 1902, 1706, 1639, 1593, 1491, 1455, 1407, 1367, 1310, 1271, 1178, 1090, 982, 822  $\text{cm}^{-1}$



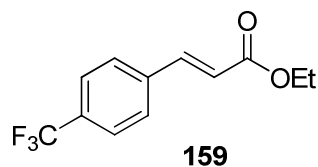
**Ethyl (*E*)-3-(4-bromophenyl)-2-propenoate 156<sup>10</sup>** (Table 16, entry 8). According to the representative **procedure A** using 4-bromo benzyl alcohol (748mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu$ L, 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.35) affording the product as a pale yellow oil (747 mg, 74%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.62 (d, 1H,  $J$  = 15.9 Hz), 7.52 (d, 2H,  $J$  = 9 Hz), 7.44 (d, 2H,  $J$  = 9 Hz), 6.42 (d, 1H,  $J$  = 15.9 Hz), 4.27 (q, 2H,  $J$  = 7.2 Hz), 1.34 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 166.7, 143.1, 133.4, 132.5, 132.1, 130.9, 129.4, 124.4, 119.0, 60.6, 14.3; FT-IR (thin film) 2981, 1711, 1638, 1588, 1488, 1403, 1366, 1310, 1271, 1174, 1072, 981, 818  $\text{cm}^{-1}$



**Ethyl (*E*)-3-(4-methoxyphenyl)-2-propenoate 157<sup>9</sup>** (Table 16, entry 9). According to the representative **procedure A** using 4-methoxy-benzyl alcohol (498  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu\text{L}$ , 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (3:1 Hexane/EtOAc  $R_f$  = 0.43) affording the product as a yellow oil (589 mg, 71%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.64 (d, 1H,  $J$  = 15.9 Hz), 7.46 (d, 2H  $J$  = 8.7 Hz), 6.90 (d, 2H,  $J$  = 8.7 Hz), 6.31 (d, 2H,  $J$  = 15.9 Hz), 4.25 (q, 2H,  $J$  = 7.2 Hz), 3.83 (s, 3H), 1.33 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 167.2, 161.2, 144.1, 129.6, 127.13, 115.7, 114.2, 60.2, 55.2, 14.3; HRMS(ESI-TOF): calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>3</sub>H<sup>+</sup>: 207.1021, C<sub>12</sub>H<sub>14</sub>O<sub>3</sub>Na<sup>+</sup>: 229.0840. Found 207.1013 (MH<sup>+</sup>), 229.0849 (MNa<sup>+</sup>); FT IR (film). 2980, 1709, 1634, 1604, 1576, 1513, 1464, 1423, 1367, 1288, 1252, 1171, 1032, 983, 828 cm<sup>-1</sup>

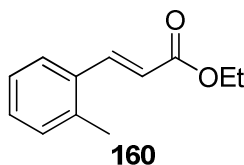


**Ethyl (*E*)-3-(4-(benzyloxy)phenyl)-2-propenoate 158<sup>11</sup>** (Table 16, entry 10). According to the representative **procedure A** using 4-benzyloxy benzyl alcohol (857mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu\text{L}$ , 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (3:1 Hexane/EtOAc,  $R_f$  = 0.47) affording the product as a white solid (931.5mg, 83%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.64 (d, 1H,  $J$  = 15.9 Hz), 7.50-7.35 (m, 7H), 6.99 (d, 1H,  $J$  = 9.6 Hz), 6.32 (d, 1H,  $J$  = 15.9 Hz), 5.10 (s, 2H), 4.26 (q, 2H,  $J$  = 7.2 Hz), 1.34 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 167.3, 160.5, 144.1, 136.5, 129.7, 128.6, 128.1, 127.4, 115.9, 115.2, 70.0, 60.3, 14.3; HRMS(ESI-TOF): calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>H<sup>+</sup>: 283.1334, C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>Na<sup>+</sup>: 305.1153. Found 283.1307 (MH<sup>+</sup>), 305.1129 (MNa<sup>+</sup>); FT-IR (nujol) 1715, 1636, 1605, 1463, 1377, 1286, 1175, 1012, 983, 748 cm<sup>-1</sup>



**Ethyl (*E*)-3-(4-(trifluoromethyl)phenyl)-2-propanoate 159<sup>9</sup>** (Table 16, entry 11).

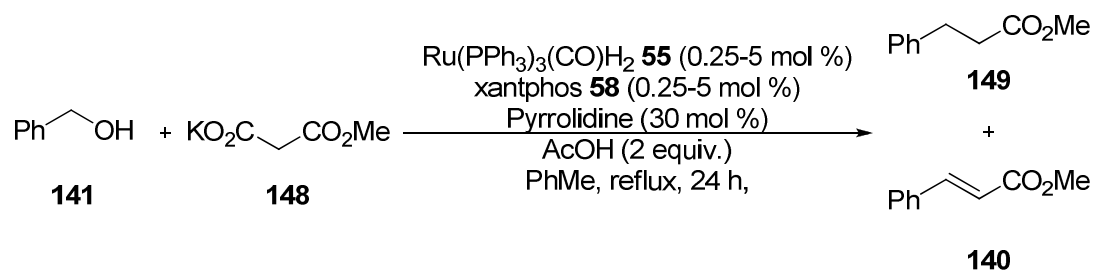
According to the representative **procedure A** using 4-trifluoromethyl-benzyl alcohol (547  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu\text{L}$ , 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 Hexane/EtOAc  $R_f$  = 0.34) affording the product as a white solid (725 mg, 74%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.73-7.61 (m, 5H) 6.51 (d, 1H  $J$  = 16.2 Hz), 4.29 (q, 2H,  $J$  = 7.2 Hz), 1.35 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 166.4, 142.7, 137.8, 128.1, 125.7 (q,  $J$  = 3.8Hz), 120.8, 60.8, 14.2; FT-IR (nujol) 1708, 1463, 1324, 1281, 1170, 1068  $\text{cm}^{-1}$



**Ethyl (*E*)-3-(*o*-tolyl)-2-propanoate 160<sup>8</sup>** (Table 16, entry 12). According to the representative **procedure A** using 2-methyl benzyl alcohol (488mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (581  $\mu\text{L}$ , 4.4 mmol, 1.1 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/diethyl ether,  $R_f$  = 0.38) affording the product as a pale yellow oil (552 mg, 73%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.89 (d, 1H,  $J$  = 15.9 Hz), 7.47 (d, 1H  $J$  = 7.2 Hz), 7.16 (m 3H), 6.25 (d, 1H,  $J$  = 15.9 Hz), 4.19 (q, 2H,  $J$  = 7.2 Hz), 2.36 (s, 3H), 1.26 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 167.0, 142.2, 137.5, 133.4, 130.7, 129.9, 126.3, 119.3, 60.4, 19.7, 14.3; HRMS(ESI-TOF): calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>H<sup>+</sup>: 191.1072. Found 191.1061 (MH<sup>+</sup>); FT-IR (film) 2980, 1712, 1634, 1601, 1486, 1366, 1313, 1275, 1220, 1177, 1036, 981, 763  $\text{cm}^{-1}$

5.4.10 Alkanes from alcohols *via* “Borrowing Hydrogen” optimisation

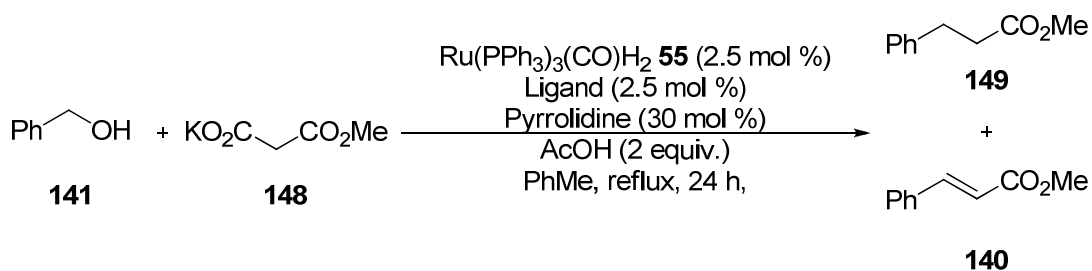
## Catalyst loading screen



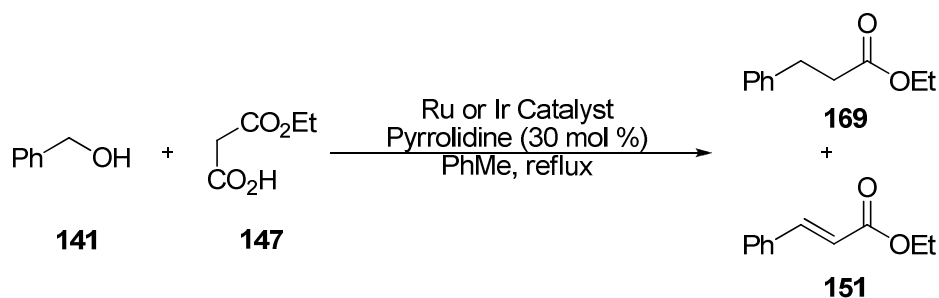
To oven dried, argon purged Radley’s carousel tubes containing  $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$  (**55**, 0.25 mol % to 5 mol % **Table 17, entries 1-5**), xantphos (**58**, 0.25 mol % to 5 mol % **Table 17 entries 1 to 5**) and pyrrolidine (25  $\mu\text{L}$ , 0.30 mmol, 0.30 equiv.) was added toluene (1 ml), benzyl alcohol (109  $\mu\text{L}$ , 1 mmol, 1 equiv), methyl potassium malonate (**148**, 234 mg, 1.5 mmol, 1.5 equiv) and acetic acid (85.8  $\mu\text{L}$ , 1.5 mmol, 1.5 equiv). The reactions were heated at reflux for 24 (or 48) hours, cooled to room temperature and the solvent was removed *in vacuo* and the crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydromethyl cinnamate **149** and methyl cinnamate **140**.



## Ligand screen

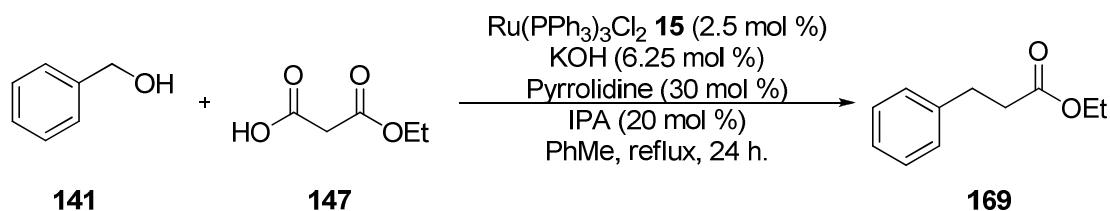


To oven dried, argon purged Radley's carousel tubes containing Ru(PPh<sub>3</sub>)<sub>3</sub>(CO)H<sub>2</sub> (**55**, 22.9 mg, 0.025 mmol, 0.025 equiv.), Ligand (2.5 mol % as outlined in **Table 18**) and pyrrolidine (25 μL, 0.30 mmol, 0.30 equiv.) was added toluene (1 ml), benzyl alcohol (109 μL, 1 mmol, 1 equiv.), methyl potassium malonate (**148**, 234 mg, 1.5 mmol, 1.5 equiv) and acetic acid (85.8 μL, 1.5 mmol, 1.5 equiv). The reactions were heated at reflux for 24 hours, cooled to room temperature and the solvent was removed *in vacuo*. The crude reaction mixture was analysed by <sup>1</sup>H NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydromethyl cinnamate **149** and methyl cinnamate **140**.

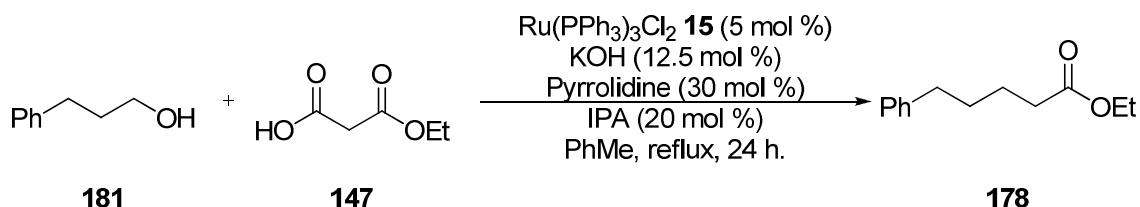
**Catalyst screen.**

To oven dried, argon purged Radley's carousel tubes containing catalysts **55**, **15** and **50** (as outline in **Table 19**), Ligand and/or base (2.5 mol % as outlined in **Table 19** with KOH loading at 6.25 mol % and Cs<sub>2</sub>CO<sub>3</sub> 10 mol %.) was added toluene (1 ml), benzyl alcohol (**141**, 109  $\mu$ L, 1 mmol, 1 equiv.) and mono ethyl malonate (**147**, 236  $\mu$ L, 2 mmol, 2 equiv) The reactions were heated at reflux for 24 hours, cooled to room temperature and the solvent was removed *in vacuo*. The crude reaction mixture was analysed by <sup>1</sup>H NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of benzyl alcohol **141**, benzaldehyde, dihydroethyl cinnamate **169** and ethyl cinnamate **151**.

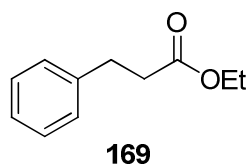
### 5.4.11 Representative procedure for the double homologation of alcohols using “borrowing hydrogen” methodology



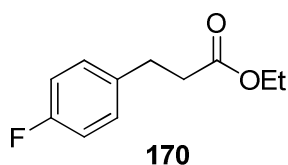
**Procedure A: Benzylic Alcohols.** To oven dried, argon purged Radley’s carousel tubes containing  $\text{Ru(PPh}_3)_3\text{Cl}_2$  (**15**, 96 mg, 0.1 mmol, 0.025 equiv.), KOH (14.4 mg, 0.25 mmol, 0.0625 equiv.) and pyrrolidine (100  $\mu\text{L}$ , 1.2 mmol, 0.30 equiv.) was added toluene (4 ml), benzyl alcohol (**141**, 436  $\mu\text{L}$ , 4 mmol, 1 equiv.), IPA (60.8  $\mu\text{L}$ , 0.8 mmol, 0.20 equiv) and monoethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.). The reactions were heated to reflux for 24 hours with a constant flow of argon, cooled to room temperature and the solvent was removed *in vacuo*. The resultant oil was purified by column chromatography.



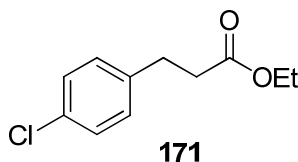
**Procedure B: Aliphatic Alcohols.** To oven dried, argon purged Radley’s carousel tubes containing  $\text{Ru(PPh}_3)_3\text{Cl}_2$  (**15**, 192 mg, 0.2 mmol, 0.05 equiv.), KOH (28.8 mg, 0.125 mmol, 0.125 equiv.) and pyrrolidine (100  $\mu\text{L}$ , 1.2 mmol, 0.30 equiv.) was added toluene (4 ml), 3-phenyl-1-propanol (**181**, 545  $\mu\text{L}$ , 4 mmol, 1 equiv.) IPA (60.8  $\mu\text{L}$ , 0.8 mmol, 0.20 equiv) and monoethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.). The reactions were heated to reflux for 24 hours with a constant flow of argon, cooled to room temperature and the solvent was removed *in vacuo*. The resultant oil was purified by column chromatography.



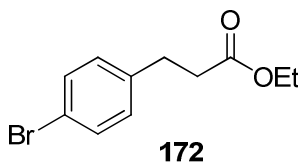
**Ethyl dihydrocinnamate 169**<sup>12</sup> (Table 20, entry 1). According to representative **procedure A** using benzyl alcohol (436  $\mu$ L, 4 mmol, 1 equiv.), mono ethyl malonate (944  $\mu$ L, 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.31) affording the product as a colourless oil (627 mg, 88%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.32-7.23 (m, 5H), 4.15 (q, 2H,  $J$  = 7.2 Hz), 2.99 (t, 2H,  $J$  = 8.1 Hz), 2.64 (t, 2H,  $J$  = 8.1 Hz), 1.26 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 173.3, 141.0, 130.6, 128.9, 128.9, 128.7, 126.6, 60.9, 36.3, 31.4, 14.6.



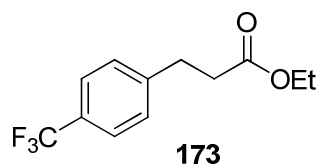
**Ethyl 3-(4-fluorophenyl)propanoate 170**<sup>13</sup> (Table 20, entry 2). According to representative **procedure A** using 4-fluorobenzyl alcohol (431  $\mu$ L, 4 mmol, 1 equiv) and mono ethyl malonate (944  $\mu$ L, 8 mmol, 2 equiv), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.35) affording the product as a colourless oil (791 mg 81%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.15 (m, 2H), 6.96 (m, 2H), 4.13 (q, 2H,  $J$  = 7.2 Hz), 2.91 (t, 2H,  $J$  = 7.5 Hz), 2.59 (t, 2H,  $J$  = 7.5 Hz), 1.22 (t, 3H,  $J$  = 7.2 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 173.0, 161.9 (d,  $^1J_{\text{CF}}$  = 244Hz), 136.6 (d,  $^4J_{\text{CF}}$  = 3.2 Hz) 130.2 (d,  $^3J_{\text{CF}}$  = 7.8 Hz), 115.6 (d,  $^2J_{\text{CF}}$  = 21.2 Hz), 60.8, 36.4, 30.5, 14.6.



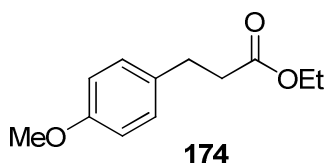
**Ethyl 3-(4-chlorophenyl)propanoate 171**<sup>13</sup> (Table 20, entry 3). According to representative **procedure A** using 4-chlorobenzyl alcohol (570  $\mu\text{L}$ , 4 mmol, 1 equiv), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/diethyl ether,  $R_f = 0.35$ ) affording the product as a colourless oil (699 mg, 82%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 7.25$  (d, 2H,  $J = 8.7$  Hz), 7.14 (d, 2H,  $J = 8.7$  Hz), 4.12 (q, 2H,  $J = 7.2$  Hz), 2.91 (t, 2H,  $J = 7.5$  Hz), 2.57 (t, 2H,  $J = 7.5$  Hz), 1.22 (t, 3H,  $J = 7.2$  Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 172.9, 139.4, 133.4, 130.1, 128.9, 61.0, 36.1, 30.5, 14.6$ .



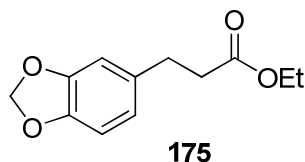
**Ethyl 3-(4-bromophenyl)propanoate 172**<sup>14</sup> (Table 20, entry 4). According to representative **procedure A** using 4-bromo benzyl alcohol (748 mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.) The title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/diethyl ether,  $R_f = 0.35$ ) affording the product as a colourless oil (741 mg, 72%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 7.41$  (d, 2H,  $J = 9.6$  Hz), 7.07 (d, 2H,  $J = 9.6$  Hz), 4.11 (q, 2H,  $J = 7.2$  Hz), 2.89 (t, 2H,  $J = 7.8$  Hz), 2.58 (t, 2H,  $J = 7.8$  Hz), 1.22 (t, 3H,  $J = 7.2$  Hz);  **$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{ppm}} = 172.9, 139.9, 131.9, 130.5, 120.4, 60.9, 36.0, 30.7, 14.6$ .



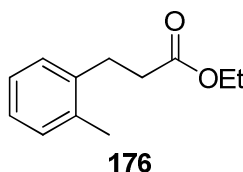
**Ethyl 3-(4-(trifluoromethyl)phenyl)propanoate 173<sup>15</sup>** (Table 20, entry 5). According to representative **procedure B** using 4-(trifluoromethyl)benzyl alcohol (547  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/diethyl ether,  $R_f = 0.35$ ) affording the product as a colourless oil (689 mg, 70%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 7.53$  (d, 2H,  $J = 8.1\text{Hz}$ ), 7.31 (d, 2H,  $J = 8.1\text{Hz}$ ), 4.12 (q, 2H,  $J = 7.2\text{Hz}$ ), 3.01 (t, 2H,  $J = 7.5\text{Hz}$ ), 2.64 (t, 2H,  $J = 7.5\text{Hz}$ ), 1.21 (t, 3H,  $J = 7.2\text{Hz}$ ); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 172.8$ , 143.0, 129.1, 129.9 (q,  $J = 32.1\text{ Hz}$ ), 125.8 (q,  $J = 3.8\text{ Hz}$ ), 124.7 (q,  $J = 270\text{ Hz}$ ), 60.9, 35.8, 31.1, 14.5.



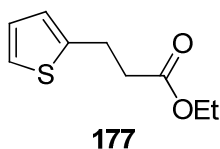
**Ethyl 3-(4-methoxyphenyl)propanoate 174<sup>15</sup>** (Table 20, entry 6). According to representative **procedure A** using 4-methoxybenzyl alcohol (498  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (3:1 Hexane/EtOAc  $R_f = 0.43$ ) affording the product as a colourless oil (598 mg, 72%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 7.12$  (d, 2H,  $J = 6.6\text{ Hz}$ ), 6.83 (d, 2H,  $J = 6.6\text{ Hz}$ ), 4.12 (q, 2H,  $J = 7.2\text{ Hz}$ ), 3.80 (s, 3H), 2.89 (t, 2H,  $J = 7.5\text{ Hz}$ ), 2.59 (t, 2H,  $J = 7.5\text{ Hz}$ ), 1.23 (t, 3H,  $J = 7.2\text{ Hz}$ ); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}} = 173.3$ , 158.5, 133.0, 129.8, 114.5, 60.7, 55.6, 36.6, 30.5, 14.6.



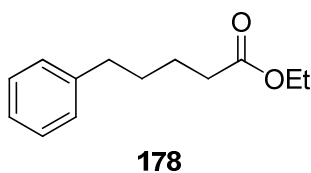
**Ethyl 3-(3,4-methylenedioxyphenyl)propanoate 175<sup>16</sup>** (Table 20, entry 7). According to representative **procedure A** using piperonyl alcohol (608 mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu$ L, 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (7:3 petroleum ether (b.p. 40-60 °C)/EtOAc  $R_f$  = 0.38) affording the product as a yellow oil (656 mg, 71%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 6.72-6.61 (m, 3H), 5.89 (s, 2H), 4.13 (q, 2H,  $J$  = 7.2 Hz), 2.85 (t, 2H,  $J$  = 7.8 Hz), 2.55 (t, 2H,  $J$  = 7.8 Hz), 1.22 (t, 3H,  $J$  = 7.8 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 173.2, 148.0, 146.3, 134.8, 121.5, 109.4, 108.6, 101.2, 60.8, 36.6, 31.1, 14.4.



**Ethyl 3-(2-methylphenyl)pentanoate 176** (Table 20, entry 8). According to representative **procedure A** using 2-methylbenzyl alcohol (488 mg, 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu$ L, 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethylether,  $R_f$  = 0.38) affording the product as a colourless oil (666 mg, 86%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 7.06-6.99 (m, 4H), 4.04 (q, 2H,  $J$  = 7.2 Hz), 2.83 (t, 2H,  $J$  = 7.5 Hz), 2.47 (t, 2H,  $J$  = 7.5 Hz), 2.22 (s, 3H), 1.14 (t, 3H,  $J$  = 7.8 Hz); **<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{ppm}}$  = 173.4, 139.1, 136.3, 130.8, 129.6, 126.8, 126.4, 65.1, 60.8, 35.1, 19.6, 14.6.

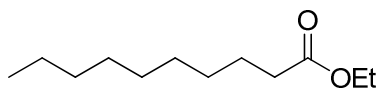


**Ethyl 3-(2-thienyl)propanoate 177** (Table 20, entry 9). According to representative **procedure A** using 2 thiophenemethanol (378  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (19:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/EtOAc  $R_f$  = 0.62) affording the product as a colourless oil (534 mg, 73%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.11 (dd, 1H,  $J$  = 1.2 Hz, 5.1 Hz), 6.91 (dd, 1H  $J$  = 3.3 Hz, 5.1Hz), 6.82 (m, 1H), 4.15 (q, 2H,  $J$  = 7.2 Hz), 3.17 (t, 2H,  $J$  = 7.5 Hz), 2.67 (t, 2H,  $J$  = 7.5 Hz), 1.23 (t, 3H,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 172.7, 143.5, 127.2, 125.1, 123.9, 60.8, 36.5, 25.5, 14.6; Anal. Calcd for:  $\text{C}_9\text{H}_{12}\text{O}_2\text{S}$ : C, 58.67; H, 6.59. Found C, 58.5; H, 6.50.

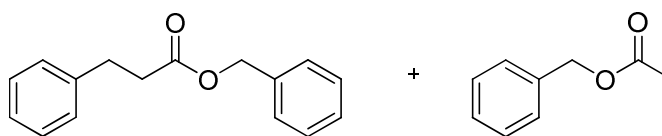


**Ethyl 5-phenylpentanoate 178**<sup>17</sup> (Table 20, entry 10). According to representative **procedure B** using 3-phenylpropan-1-ol (545  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60  $^{\circ}\text{C}$ )/diethyl ether  $R_f$  = 0.36) affording the product as a colourless oil (642 mg, 77%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.33-7.18 (m, 5H), 4.19 (q, 2H,  $J$  = 7.2 Hz), 2.64 (t, 2H,  $J$  = 8 Hz), 2.32 (t, 2H,  $J$  = 8 Hz), 1.70 (m, 4H), 1.33 (t, 3H,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 174.0, 142.6, 128.7, 126.4, 60.6, 35.9, 34.8, 31.3, 25.0, 14.7.



**179**

**Ethyl decanoate 179 (Table 20, entry 11).** According to representative **procedure B** using 1-octanol (630  $\mu\text{L}$ , 4 mmol, 1 equiv.), and mono-ethyl malonate (944  $\mu\text{L}$ , 8 mmol, 2 equiv.), the title compound was synthesised and purified by bulb to bulb distillation (bp 105°C, 5mm Hg) affording the product as a colourless oil (596 mg, 75%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 4.04 (q, 2H,  $J$  = 7.2 Hz), 2.18 (t, 2H,  $J$  = 7.5 Hz), 1.51 (m, 2H), 1.22 (m, 15H), 0.81 (t, 3H,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 172.9, 59.1, 33.4, 30.9, 28.3, 24.0, 21.7, 13.1.

**180**

**Benzyl dihydrocinnamate 180<sup>18</sup> (Table 20, entry 12).** According to representative **procedure A** using benzyl alcohol (436  $\mu\text{L}$ , 4 mmol, 1 equiv.), mono benzyl malonate (1.55 g, 8 mmol, 2 equiv.), the title compound was synthesised and purified by column chromatography (9:1 petroleum ether (b.p. 40-60 °C)/diethyl ether,  $R_f$  = 0.38) as a colourless oil (1.25 g) containing benzyl acetate as a by product which co-eluted. Analysis of the  $^1\text{H}$  NMR revealed a 3:2 ratio of product to benzyl acetate equating to 880 mg of product and 367 mg of benzyl acetate, corresponding to a 92% conversion to product.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 7.37-7.24 (m, 7H), 7.21-7.16 (m, 3H), 5.10 (s, 2H), 2.96 (t, 2H  $J$  = 7.4 Hz), 2.67 (t, 2H  $J$  = 7.4 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{ppm}}$  = 172.8, 136.1, 128.8, 128.7, 128.5, 126.5, 66.7, 36.3, 31.4.

**5.5 References**

1. Ahmad, N.; Levison, J. J.; Robinson, S. D.; Uttley, M. F., *Inorg. Synth.* **1974**, 15, 45
2. Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A., *Org. Lett.* **2007**, 9, 953.
3. Molander, G. A.; Canturk, B.; Kennedy, L. E., *J. Org. Chem.* **2009**, 74, 973.
4. Babudri, F.; Cicco, S. R.; Farinola, G. M.; Lopez, L. C.; Naso, F.; Pinto, V., *Chem. Commun.* **2007**, 3756.
5. De, S. K., *Catal. Lett.* **2007**, 124, 174.
6. Chen, J. X.; Liu, M. C.; Yang, X. L.; Ding, J. C.; Wu, H. Y., *J. Braz. Chem. Soc.* **2008**, 19, 877.
7. Zeitler, K., *Org. Lett.* **2006**, 8, 637.
8. Duguet, N.; Harrison-Marchand, A.; Maddaluno, J.; Tomioka, K., *Org. Lett.* **2006**, 8, 5745.
9. Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P., *J. Org. Chem.* **2003**, 68, 3714.
10. Couladouros, E. A.; Soufli, I. C.; Moutsos, V. I.; Chadha, R. K., *Chem. Eur. J.* **1998**, 4, 33.
11. Reddy, S. H. K.; Lee, S.; Datta, A.; Georg, G. I., *J. Org. Chem.* **2001**, 66, 8211.
12. Chandrasekhar, S.; Reddy, G. P. K.; Nagesh, C.; Reddy, C. R., *Tetrahedron Lett.* **2007**, 48, 1269.
13. Nestl, B. M.; Glueck, S. M.; Hall, M.; Kroutil, W.; Stuermer, R.; Hauer, B.; Faber, K., *Eur. J. Org. Chem.* **2006**, 4573.
14. Zaidlewicz, M.; Wolan, A. *J. Organomet. Chem.* **2002**, 657, 129..
15. Amatore, M.; Gosmini, C.; Perichon, J., *J. Org. Chem.* **2006**, 71, 6130.
16. Makhey, D.; Li, D.; Zhao, B. P.; Sim, S. P.; Li, T. K.; Liu, A.; Liu, L. F.; LaVoie, E. J., *Bioorg. Med. Chem.* **2003**, 11, 1809.
17. Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M., *J. Org. Chem.* **1998**, 63, 2755.
18. Black, P. J.; Edwards, M. G.; Williams, J. M. J., *Eur. J. Org. Chem.* **2006**, 4367.